

FORMULATION AND EVALUATION OF FAMOTIDINE BEADS AS CONTROLLED DRUG DELIVERY SYSTEM

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INTRODUCTION

ORAL DRUG DELIVERY SYSTEM

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience, and cost effective manufacturing process. For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with acceptable level of safety to the patient. In recent years a wide variety of newer oral drug delivery systems like sustained/controlled release dosage forms are designed and evaluated in order to overcome the limitations of conventional therapy. These products are able to maintain steady drug plasma levels for extended periods of time as a result the variations of the drug levels in the blood are prevented and minimized drug related side effects.¹

For many decades treatment of an acute disease or chronic illness has been mostly accomplished by delivery of drugs to the patients using various pharmaceutical dosage forms, including tablet, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables, as drug carriers. Even today these conventional drug delivery systems are the primary pharmaceutical product commonly seen in the prescription and over-the-counter drug market place. This type of drug delivery system is known to provide a prompt release of drug. Therefore, to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day. This results in a significant fluctuation in drug levels.²

Recently, several technical advancements have been made. They have resulted in the development of new technique for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and or targeting the drug to a tissue. Although these advancements have led to the

developments of several novel drug delivery systems that could revolutionize the method of medication and provide a number of therapeutic benefits.

For many disease states, the ideal dosage regimen is one in which an acceptable therapeutic concentration of the drug is immediately attained at the site of action and is maintained constant for the desired duration of treatment. Conventional dosage systems release the complete drug immediately after its administration. Their kinetic pattern is as follows in figure 1.1.³

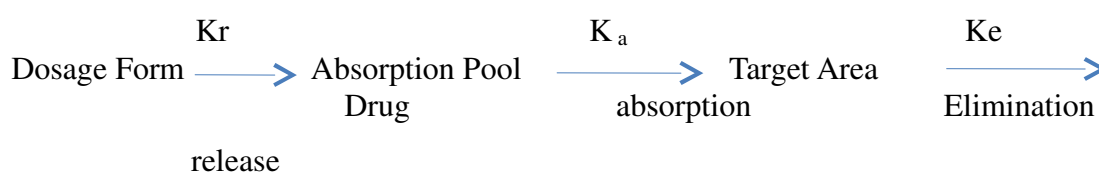


Figure 1-1: Conventional order rate constants for drug release

These systems have limitations including ⁴

1. Plasma concentration fluctuations over successive dosing intervals.
2. For drugs having short biological half-lives, frequent doses are required to maintain the steady state plasma concentrations within the therapeutic range.
3. Thus, for such drugs, maintaining a therapeutic plasma concentration becomes a problem especially in the case of missing doses and the overnight no dose period.
4. The drug levels may not be within the therapeutic range at sufficiently early times. This is an important consideration for certain disease states.
5. Patient noncompliance with a multiple dosing regimen can result in the failure of this therapeutic approach.

The absorption pool has drug available already in solution and ready for absorption at the site of absorption. The k_r , k_a , and k_e are first order rate constants for drug release, absorption, and overall elimination, respectively. Immediate release from a conventional dosage forms has $k_r \gg k_a$. For non-immediate release dosage forms $k_r \ll k_a$ (i.e., the release of the drug from the dosage form is the rate limiting step). The kinetic pattern is seen in Figure 1.2



Figure 1-2: Non immediate release dosage pattern

Types of Non Immediate Release Dosage Forms⁴

A non-immediate release dosage form alters the release rate by affecting the value of k_r . A non-immediate release dosage form may be conveniently divided into four categories:

- 1) Delayed release
- 2) Sustained release
 - a) Controlled release
 - b) Prolonged release
- 3) Site specific release
- 4) Receptor release

Delayed release employs a repetitive, intermittent dosing of drugs from one or more immediate release units incorporated into a single dosage form. These types of dosage forms include repeat action tablets and capsules, and enteric coated tablets where timed release is achieved by barrier coating.

Sustained release dosages are drug delivery systems that achieve slow release of the drug over an extended period of time.

If the system is successful in sustaining a constant drug level in the body or target tissue, it is considered a controlled release system.

If it is unsuccessful in providing a constant level, but extends the duration of action over that which is achieved by conventional delivery, it is known as prolonged release system.

Site specific and receptor release refers to the targeting of a drug directly to a certain biological location. For site specific release, the target should be a certain organ or tissue. For receptor release, the target should be the particular receptor for a drug within an organ or tissue.²

Oral Controlled release Drug Delivery Systems¹

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action. All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate,

sustained or controlled release) and the design of dosage form (solid, dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of

- (i) physicochemical, pharmacokinetic and pharmacodynamics characteristics of the drug;
- (ii) The anatomic and physiologic characteristics of the gastrointestinal tract and
- (iii) Physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

The several advantages of a controlled drug delivery system over a conventional dosage forms:

- Total dose is low
- Reduced GI side effect
- Reduced dosing frequency
- Better patient acceptance and compliance
- Less fluctuation at plasma drug levels
- More uniform drug effect
- Improved efficacy/safety ratio

Disadvantages

- Dose dumping
- Stability problem
- Reduced potential for accurate dose adjustment
- Need of additional patient education

The main areas of potential challenge in the development of oral controlled drug delivery systems are: ¹

- Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.
- Modulation of gastrointestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.

- Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.¹

ANATOMY AND PHYSIOLOGY OF GASTRO INTESTINAL TRACT AND DRUG DELIVERY. ⁵

Systems used for the delivery of therapeutic agents via the oral route must be designed conscious of the physiology of the gastrointestinal tract. The anatomy and physiology of route of administration may dictate many of the requirements for the systems. For example, the device must be able to withstand the saliva, as saliva contains digestive enzymes and other reagents for breaking down whatever is placed in the mouth. The stomach, the main digestive organ of the body, contains many digestive enzymes and very low pH. The pH of the stomach has been measured from 1.4 to 2.1. This harsh environment causes the destruction and denaturation of proteins without protection. The pH of the stomach changes when food is present increasing to nearly 4.0 (Dressman *et al.*, 1990).

Once through the harsh conditions of the stomach a device reaches the small intestine, which is divided into three regions. The first region, closest to the stomach, is the duodenum, followed by the jejunum and ileum. The duodenum is about 10 inches in length, composes 5% of small intestine and jejunum composes 40% of the length of the small intestine. The entire length of the small intestine is 5 meter and residence time within the organ typically ranges from 2-4 h.

Microparticles smaller than 10 μm are transported to the Payer's patches of the gut associated lymphoid tissue (GALT) (Eldridge *et al.*, 1990; Smith *et al.*, 1995 and Janiet *et al.*, 1992). The GALT is represented by the Payer's patches (PPs), the appendix and small solitary lymphoid nodules. The dome regions of the PPs contains lymphocytes, macrophages and some plasma cells and is covered by the follicle associated epithelium which is specialised in the uptake of antigens from foods. The cells responsible for the actual uptake of viruses, bacteria, toxins and microparticles smaller than 10 μm are the microfold cells (M-cells) (Lydyard and Grossi, 1998; Eldridge *et al.*, 1990). These M cells differ in morphology from absorptive cells by their short microvilli, small cytoplasmic vesicles and few lysosomes. Fig1.3 gives an overall idea about GIT and protein digesting enzymes involved in GIT.

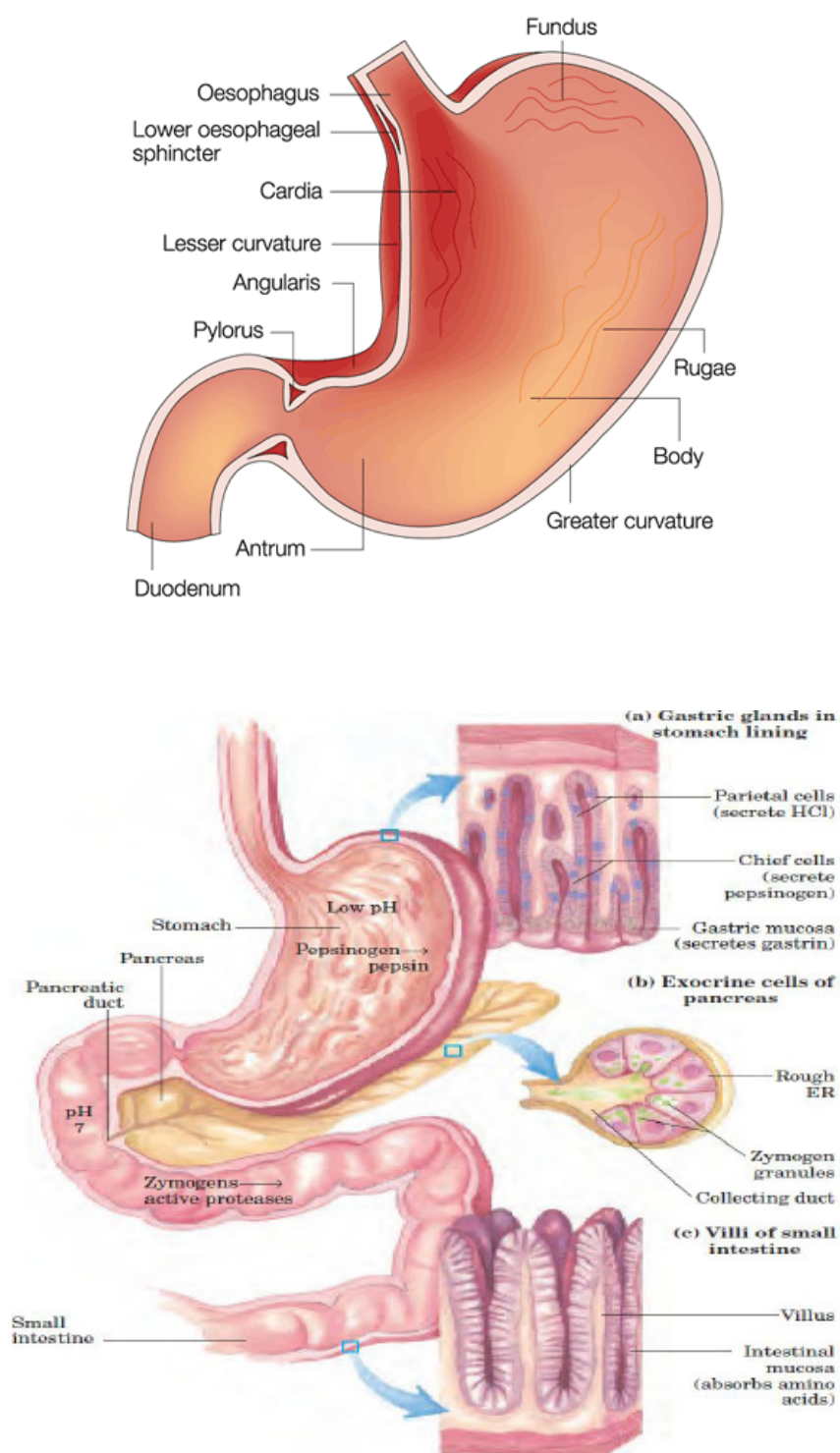


Fig1.3 gives an overall idea about GIT.

Human intestinal tract (lehninger principles of biochemistry, 2008).

The lining of the small intestine are composed of the serous, muscular, areolar, and mucous layers. Only the mucous and areolar layers are the important layers with respect to drug delivery. Transport of the nutrients into the body occurs through the mucous cell layer and into the areolar layer where the nutrients are taken into the blood stream. In the mucosal layer, there are cell layers that stick out of it and into the open areas of the duodenum.

Table 1.1: Gastro intestinal tract: Physical Dimension and Dynamics.

Region	Surface area(m ²)	Length(m)	Transit time	
			Fluid	Digestive solid
GIT	200	----	----	----
Stomach	0.1-0.2	----	50 min	8 h
Small intestine	100-4500	3.0	2-6 h	4-9 h
Large intestine	0.5-1.0	1.5	2-6 h	3h -3days

Drug Release from Controlled Oral Dosage Form .²

The purpose of a sustained release system is to deliver a drug at a rate necessary to achieve and maintain a constant drug blood level. This means that the rate of delivery should be independent of the amount of drug remaining in the dosage form and constant over a certain time. It implies that the rate should follow zero order kinetics. Zero order release may be theoretically desirable. Non zero order release rates may be clinically equivalent to constant release in many cases.⁵⁰

In order to achieve a therapeutic level promptly and maintain that level for a given period of time, the dosage form generally should consist of two parts.

With controlled oral dosage forms, the total drug in the dosage form should consist of two portions, a loading dose and a maintenance dose. The initial loading dose is released immediately on its administration. The release of the drug is characterized by a first order kinetic process. The loading dose immediately obtains the acceptable therapeutic plasma levels. The remaining dosage is released at a slow

and a controlled rate in order to maintain the constant plasma concentration of the drug.

The release pattern has to follow zero order kinetics. Therefore, the rate of release of the drug is independent of the remaining fraction of the dose. The controlled oral dosage form involves releasing the maintenance dosage at a rate which is equivalent to the elimination rate of the drug.

Methods of Preparing Controlled Oral Dosage Forms

A number of formulation methods have been developed to overcome the barrier seen with immediate release oral dosage forms. These processes include: inert insoluble matrices; use of coatings; hydrophilic matrices; as well as the combination of hydrophilic and hydrophobic polymers (5); embedding of the drug in a wax or plastic matrix; ion exchange resins; osmotic pumps; and microencapsulation. The physiology of the gastrointestinal tract, the physico-chemical property of the drug, the drug release pattern, the pharmacological action of the drug, is parameters that must be considered. The 6 physico-chemical properties of the drug involve such parameters as: aqueous solubility; stability; p^{Ka} and permeability values.²

The Biopharmaceutical Classification System (BCS) involves placing a drug into four classifications (6): ¹

1. High solubility and high permeability
2. Low solubility and high permeability
3. High solubility and low permeability
4. Low solubility and low permeability

Class 1 is considered the preferred category while Class 4 is the worst category. A drug having high solubility in the intestine is a good drug for a controlled oral dosage form. The drug permeability value must also be considered and should be more than the prescribed value. The drug having a biological half-life of between two and six hours is the preferred drug because we want to avoid accumulation of the drug in the body.

Multiparticulate dosage form²

Multiparticulate dosage form contains actives divided into many individual units, so-called subunits, each exhibiting some desired characteristics. These subunits usually are microparts such as microcapsules, microspheres, lipospheres, microgranules or larger particles - pellets. Multiparticulate dosage forms are more expensive to manufacture and develop, but despite of it are widely used in

pharmaceutical formulations. They are more reliable in their biopharmaceutical behavior and considered to provide pharmacokinetic advantages compared

With monolithic dosage forms

When compared with single-unit dosage forms, oral multiparticulate drug-delivery systems offer biopharmaceutical advantages:

- Micro particles can be used to prepare pharmaceutical formulations composed of Incompatible drugs or to obtain delivery systems with different release profiles.
- Can be divided into desired doses without formulation and process changes.
- Possibility to produce modified release dosage forms as very significant means of drug delivery now a day.
- More even and predictable distribution and transportation in the gastrointestinal tract, which is fairly independent of the nutritional state .When taken orally multiparticulates generally disperse freely in the gastrointestinal tract, thus maximize drug absorption, reduce peak plasma fluctuation, minimize side effects and reduce inter and intra patient variability
- Are less susceptible to dose dumping than the reservoir-type, single unit formulations. These dosage forms have several disadvantages, like the risk of tampering with capsules or

The rupturing of the coating during compression resulting in a loss of the modified drug-release Properties .⁶

Two general structures exists – Microcapsules and Microparticles¹

Microcapsules are a system that contains a well-defined core and a well-defined envelop. The core can be solid, liquid or gas; the envelope is a made of a continuous, porous or non-porous, polymeric phase. The drug can be dispersed inside the microcapsule as solid particulates with regular or irregular shapes, pure or dissolved solution, suspension, emulsion or a combination of suspension and emulsion¹

A micro particle is a structure made of a continuous phase of one or more miscible polymers in which particulate drug are dispersed at either the macroscopic or molecular levels. However, difference between the two systems is the nature of the micro particle matrix in which no well -defined wall or envelop exists.

The term microcapsule is defined as a spherical particle with size varying from 50nm to 2 mm, containing a core substance. Microspheres are in strict sense, spherically empty particle. However, the term microcapsule and microsphere are often used synonymously. In addition, some related terms are used as well. For example “**microbeads**” and beads are used alternatively.

Microencapsulation has become a common technique in the production of controlled release dosage forms. One approach for controlled release formulation of different therapeutic agents is the production of **polymeric gel beads**. The beads are discrete spherical microcapsules that serve as the solid substrate on which the drug is coated or encapsulated in the core of the beads. Beads can provide sustained release properties and more uniform distribution of drugs include, within the gastrointestinal tract. Furthermore, bioavailability of drugs formulated in beads has been enhanced. Numerous studies have been reported, concerning the use of alginate beads as a controlled release carrier. Formulation of cardiovascular drug in beads forms could reduce its dosing frequency. Hence, in this study the formulation of Calcium alginate cardiovascular drug beads, through ionotropic gelation and cross linking method has been investigated.⁷

On the basis of classification these microcapsules and microspheres are prepared by following techniques:

- Single emulsion technique
- Double emulsion technique
- Polymerization technique
- Normal polymerization technique
- Interfacial polymerization technique
- Phase separation coacervation technique
- Spray drying & spray congealing technique
- Solvent extraction technique
- Solvent evaporation technique
- Solvent diffusion technique
- Ionotropic gelation technique

Release characteristics of gel beads⁸

Release of core material from non-erodible microbeads can occur in several ways. Non-erodible spherical microbeads release the encapsulated material by steady-state diffusion through a coating of uniform thickness. The rate of release remains constant as long as the internal and external concentration of core material and concentration gradient through the membrane are constant. If some of the encapsulated material migrates through the microcapsule membrane during storage a burst effect occurs. If the microcapsule acts as inert matrix particle in which core material is dispersed (microparticles) the Higuchi model is valid up to 60% release.

Microencapsulation by Ionotropic Gelation Technique

In this method strong spherical beads with a narrow particle size distribution and low friability could be prepared with high yield and a drug content approaching 91.25 %. The flow properties of micronized or needle like drug crystals were significantly improved by this agglomeration technique when compared with non-agglomerated drug crystals. The ionic character of the polymers results from pH dependent disintegration of the beads.⁶

One of the most important and useful properties of alginates is the ability to form gels by reaction with calcium salts. Alginic acid is composed of D-mannuronic acid and L-gluronic acid residues at varying proportions of GG-, MM- and MG-blocks. Crosslinking takes place only between the carboxylate residue of GG-blocks and Ca^{+2} ions via egg-box model to give a tight gel network structure. These gels resemble a solid in retaining their shape and resisting stress and consist of almost 100% water.

A gel in classical colloidal terminology is defined as a system which owes its characteristic properties to a cross-linked network of polymer chains which form at the gel point. A considerable amount of research has been carried out in recent years to elucidate the nature of the cross-links and determine the structure of alginate gels. It has been suggested that the cross-links were caused either by simple ionic bridging of two carboxyl groups on adjacent polymer chains via calcium ions or by chelating of a single calcium ions by hydroxyl and carboxyl groups on each of a pair of polymer chains.⁴

Polymers used for the preparation of microbeads.⁸

A number of Different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microbeads. These materials include the polymers of natural and synthetic origin and also modified natural substances. Some examples of polymers are Albumin, Gelatin, Sodium alginate, Chitosan, Starch, Dextran, Poly lactide and olyglycolide Polyanhydride, Polyphosphazene etc.

Sodium alginate micro beads

Beads are one of the multiparticulate drug delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites. Multiple unit dosage forms such as microspheres or beads have gained in popularity as oral drug delivery systems because of more uniform distribution of the drug in the gastrointestinal tract, more uniform drug absorption, reduced local irritation and elimination of unwanted intestinal retention of polymeric material, when compared to non-disintegrating single unit dosage form.⁹

Beads can also offer advantages like

- Limiting fluctuation within therapeutic range,
- Reducing side effects,
- Decreasing dosing frequency.
- Improving bioavailability.
- Improving patient compliance.

Alginates are naturally occurring polysaccharides obtained mainly from marine brown algae belonging to the Phaeophyceae, composed of two monomeric units, β -D-mannuronic acid and α -L-guluronic acid. Alginate salts are known to form a reticulated structure when in contact with calcium ions and this characteristic has been used to produce sustained release particulate systems for a variety of drugs, proteins and even cells. The gel forming ability is related mainly to the proportion and arrangements of mannuronic to guluronic acid units present. Calcium Alginate beads can be produced by dropping a sodium alginate aqueous solution into a calcium chloride solution. Although this is a simple and fast way of obtaining particulate drug carriers, the method presents a major limitation consisting of drug loss during bead preparation. In addition, the calcium alginate matrix formed is usually very permeable

and little or no drug release can actually be controlled in the case of soluble drugs [4, 5]. Hence, a preferential use for alginate gel beads in the delivery of low solubility or macromolecular drugs has been suggested, while some researchers were able to circumvent this problem by mixing alginate with other polymers such as pectin, chitosan, ethyl cellulose and Eudragit. Successful attempts involving the cross-linking of sodium alginate alone or with albumin or gelatin, using aldehydes, have also been reported. However, the techniques utilized in these studies either may cause a high degree of particle aggregation or involve the use of methanol as a solvent.¹⁰

Gelation Properties ⁴

In the presence of certain divalent and multivalent cations. For example Ca^{2+} , alginates form gels. The properties of these gels depends upon the mannuronic acid to guluronic acid ratio (M: G ratio) of the alginate. Alginates with a high guluronic acid content Form strong brittle gels, whereas those with a high mannuronic acid content form weaker but more flexible gels. There are only minor differences in the structure of the two monomers and their affinity for divalent cations, thus the large difference seen in ion-binding by poly-guluronate and poly-mannuronate groups must have a macromolecular explanation. In order that the bulky carboxyl group is in the energetically favored equatorial position, the two uronic acids will adopt different preferred conformations. Thus, mannuronic acid adopts the $4C_1$ chair conformation and guluronic acid adopts the $1C_4$ boat form Evidence from X-ray diffraction studies supports this theory.

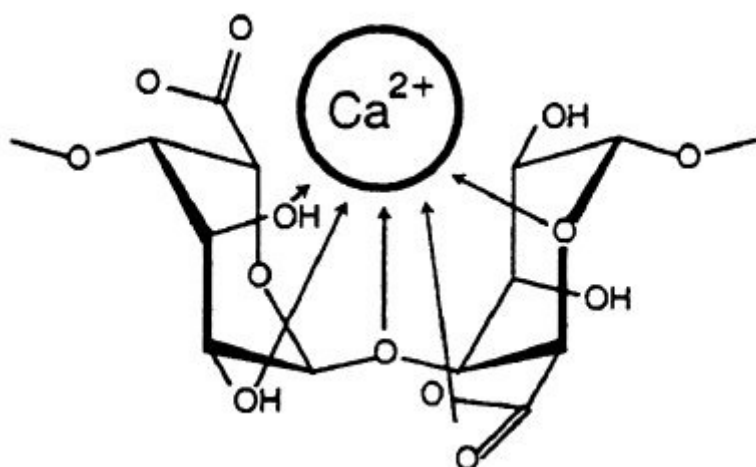


Figure 1.4 Gelation properties of sodium alginate

The orientation of the glycosidic bonds between the monomers will then affect the conformation of the polysaccharide chain. Therefore, it has been predicted (Rees 1972), that regions in which poly-D- mannuronate predominates (M-M-M) will form an extended ribbon structure (Figure 1.4), similar to that of cellulose. Whereas, the region in which poly-L-guluronate predominates (G-G-G) will form a buckled chain (Figure 1.4). Further X-ray diffraction experiments by Atkins et al (1973a and 1973b); together with solution studies using ^1H -NMR (Penman and Sanderson 1972), and ^{13}C -NMR (Grasdalen et al 1977) provide evidence to confirm this prediction.

The mode of binding of Cations by the various block structures within the alginate explains why the gels formed have different properties depending on the ratio of D-mannuronate to L-guluronate (M:G ratio). All the block structures are poly anionic and will form intermolecular bonds with divalent or multivalent cations, such as Ca^{2+} . However, poly-guluronate regions are also able to chelate the metal ion because of the spatial arrangement of the ring and hydroxyl oxygen atoms, there by forming a much stronger type of interaction. Cavity-like sites are formed between adjacent G-units into which ions such as Ca^{2+} fit well (Figure 1.6). Thus, two or more chains may be joined together, side by side, by salt bridge formation Between the G-blocks. This has been likened to the cross-section of an 'egg-box' (Grant et al 1973) as shown in Figure 1.7, where the Ca^{2+} ions are the 'eggs' within the 'egg-box'-like cross section of the alginate chains.

For this reason, when controlled amounts of calcium are added to alginate solutions, gels are formed. The calcium ions bind strongly to the G-blocks, but the formation of an insoluble precipitate is prevented by the presence of the M -blocks and the MG-blocks where the interaction with calcium ions is less. Since most alginates contain all three types of block structure (M, G, and MG), a classical gel structure can be formed where the G-blocks from the junction zones which are terminated by regions of M-blocks or MG-blocks. These remain dissolved and keep the system in solution as a hydrated three-dimensional network. There by Forming a gel.

Extraction and Preparation: Since alginates occur in the form of insoluble calcium, magnesium, sodium and potassium salts contained in the algal cell walls and the extra cellular matrix, their extraction and purification generally involve ion

exchange techniques; the details of the extraction methods are given in figure 1.5. Generally to prepare alginates for commercial use, the algae is mechanically harvested and dried before further processing except for *M. Pyrifera* which is processed in wet. Alginates are then extracted from dried and milled algal material after treatment with dilute mineral acid to remove or degrade associated neutral homo polysaccharides such as laminarin and fucoidin. Concurrently the alkaline earth cations are exchanged for H⁺. The alginate is then converted from the insoluble proteonated form to the soluble sodium salt by addition of sodium carbonate at a PH below 10. After extraction, the alginate can be further purified and then converted to either a salt or acid .

Therapeutic applications of sodium alginate beads.¹⁰

The alginate, chitosan or alginate-chitosan beads can have various therapeutic uses depending upon the drug loaded into them.

1. NSAIDs like Diclofenac sodium may be made into beads which show reduced release in the acidic environment of the stomach. This minimizes the adverse effects of oral administration and avoids direct contact between the drug and the gastric mucosa. ¹ The other NSAID, ibuprofen, may also be the candidate for the prolonged and the controlled release formulation because of its short half- life and gastric irritation activity both of which can easily be overcome by using the alginate beads.
2. The beads loaded with the antibiotics (like ampicillin) may be useful for the oral delivery for the treatment of gastric and intestinal diseases. The sustained and the controlled release of ampicillin may be useful to overcome its short biological half-life of 0.75-1.5 hours.
3. Antihypertensive drugs, like verapamil HCl, with low bioavailability due to first pass metabolism may be formulated in the alginate chitosan beads so that their controlled release may be obtained for the prolonged therapeutic effect. Another antihypertensive calcium channel blocker, Nicardipine, may be a candidate for the controlled release beads as it has a very short half- life of 1 hour.

4. The sustained release dosage form which delivers melatonin over the period of 8 hours may be useful for those who have disordered circadian rhythm and that could be maintained through the use of polymer reinforced and coated alginate beads. Melatonin has short half-life so is not very effective as immediate release dosage form
5. Sustained release of prednisolone from chitosan gel beads allows minimum effective dose to be delivered locally (subcutaneous) and prolongs the duration of drug activity. So, it improves the therapeutic efficacy and decreases side effects by minimizing the transportation of the drug to the systemic circulation against inflammation.
6. Theophylline, a poorly water soluble bronchodilator and the targeted drug for sustained delivery, showed the retarded drug release under physiologically simulated pH conditions (acidic and neutral). So, it could be a good candidate for the modified dosage forms
7. Ketoconazole, an antifungal drug, may be formulated into the polymeric beads to reduce the adverse effects like hepatic dysfunction and GI disturbances which are generally observed with conventional oral dosage forms.
8. Cefadroxil, an antibiotic used in the treatment of bacterial infections, has a biological half-life of 1.2-2.0 hours. Its short half-life may be enhanced by the use of the sodium alginate interpenetrating network beads.
9. Insulin, an anti-diabetic polypeptide drug, and albumin are degraded in the acidic medium when given orally. Formulating them in the modified alginate beads may deliver them in the intestinal region without significant degradation in the stomach.
10. Brilliant blue (poorly water soluble dye) showed the extended release and dextran (water soluble polysaccharide) showed a faster release indicating that the water insoluble drugs may be used for the controlled delivery.
11. Alginate-chitosan beads containing nicotinic acid and ascorbic acid (a water soluble vitamin), drugs for hyperlipidemia, show controlled release of these

drugs. Bile acids are responsible for the breakdown and the absorption of the fatty substances. The beads may also be useful in absorbing the bile acids and may prove to be very valuable in treatment of hyperlipidemic patients.

12. Unpredictable and incomplete absorption limits the oral delivery of 5-fluorouracil, an anticancer drug. So their local use in the treatment of breast cancer may be justified in polymeric bead forms.

13. Metronidazole, an antiulcer drug, in bead form to be retained in stomach for sufficient time to exert anti *Helicobacter pylori* effect. The gastro-retention of the drugs, especially antiulcer and antacid, by formulating them in the floating beads, could open new doors for the treatment of gastric ulcer and acidity.

Gastric emptying:

The process of gastric emptying occurs during fasting as well as fed states. However, the pattern of motility is distinct in the 2 states. In the fasting state, it is characterized by an interdigestive series of electrical events that cycle both through stomach and small intestine every 2 to 3 hours ¹¹. This activity is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 consecutive phases as described by Wilson and Washington¹².

Phase I (basal phase): it is a quiescent period lasting from 40 to 60 minutes with rare contractions.

Phase II (preburst phase): it is period of similar duration lasting for 40 to 60 minutes consisting of intermittent action potentials and contractions that gradually increases in intensity and frequency as the phase progresses.

Phase III (burst phase): it is a short period of intense, large regular contractions lasting for r 4 to 6 minutes. It is this phase, which gives the cycle the term, housekeeping wave, since it serves to sweep undigested materials out of the stomach and down the small intestine.

As phase III of one cycle reaches the end of the small intestine, phase III of the next cycle starts I the duodenum.

Phase IV: it is a brief transitional phase that occurs between phase III and phase I of their two Consecutive cycles. The motor activity in the fed state is induced 5-10 min after ingestion of a meal and persists as long as food remains in the stomach.

It consists of regular and frequent contractions. These contractions are not as severe as those in the third phase of the fasted motility pattern ¹³.

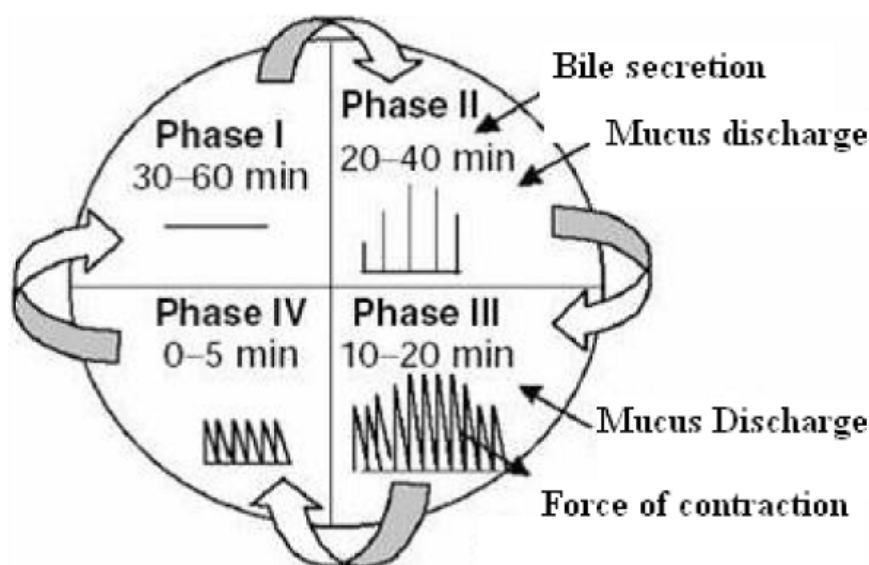


Fig.2.Schematic representation of interdigestive motility.

1.4: Factors Affecting Gastric Retention.

Density: GRT is a function of dosage form buoyancy that is dependent on the density of a dosage form which affects the gastric emptying rate. A buoyant dosage form should have a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.

Size: Dosage form units having a diameter of more than 7.5 mm are reported to have an increased gastric residence time compared with those having a diameter of 9.9 mm. Gastric retention time of an dosage form in the fed state can also be influenced by its size. Small tablets are emptied from the stomach during the digestive phase while large .size units are expelled during the house keeping waves ^{14,15}.

Shape of dosage form: The six shapes tested (ring, tetrahedron, cloverleaf, disk, string and pellet) displayed different gastric retention times, due to their size and geometry of the systems ¹⁶.The tetrahedron resided in the stomach for longer periods than other devices of a similar size; likewise extended gastric retention was observed with rigid rings .Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) have a better gastric residence time as

compared with other shapes and had been reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.

Single or multiple unit formulation: multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

Effect of buoyancy: On comparison of floating and nonfloating dosage units, it was concluded that regardless of their sizes the floating dosage units remained buoyant on the gastric contents throughout their residence in the gastrointestinal tract, while the nonfloating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during digestive phase while the nonfloating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase.

FOOD HABITS AFFECT THE GRT IN THE FOLLOWING WAYS:

Fed or unfed state: under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer. It was concluded that as meals were given at the time when the previous digestive phase had not completed, the floating form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach.

Nature of meal: feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

Caloric content: GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

Frequency of feed: the GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender: mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface ¹⁷.

Age: elderly people, especially those over 70, have a significantly longer GRT.

Posture: GRT can vary between supine and upright ambulatory states of the patient. When subjects were kept in the supine position it was observed that the floating forms could only prolong their stay because of their size; otherwise the buoyancy remained no longer an advantage for gastric retention.

Biological factors: diabetes and Crohn's disease, Etc.

Concomitant Drug administration & interaction: anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.

In order for a hydrodynamically balanced dosage forms to float in the stomach. The density of the dosage forms should be less than the gastric contents. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyant capabilities¹⁴. The prolongation of the gastric residence time by food is expected to maximize during drug absorption from the dosage form due to increased dissolution of the drug and longer residence at the most favourable sites of absorption. However, literature data on the relationship between device size and gastric residence time are contradictory ¹⁸⁻²⁰.

1.5 : Absorption window:

The G.I tract offers a varied environment capable of affecting the absorption of poorly administered drugs. Anatomical features, physiological phenomenon, and nature of gastrointestinal milieu contributes these changes. This can lead to the variations in the intestinal permeability of drug molecules, resulting in the phenomenon of Absorption window, where in the drug is preferentially absorbed only from a particular region of the G.I.tract.

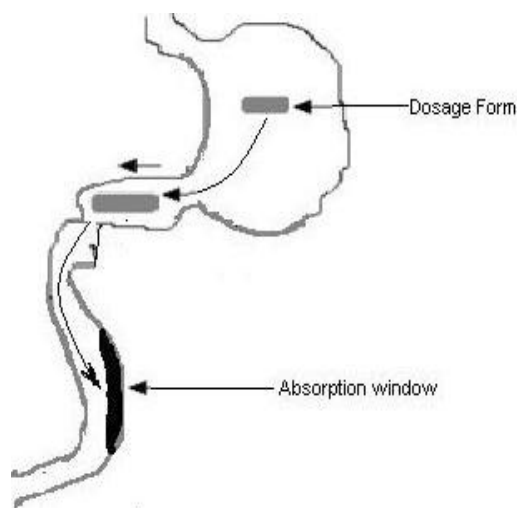


Fig.3. Absorption window in G.I. tract.

1.5.1. ABSORPTION WINDOW COULD RESULT FROM THE FOLLOWING FACTORS:

1.5.1.1. Physico-chemical factors:

PH- dependent solubility and stability:

A drug experiences a pH range of 1-8 across the G.I tract and needs to be in solubilised form to successfully cross the biological membrane. Most of the drugs are passively absorbed, in their un-ionized form and the extent of ionization at different pH dependent solubility, stability and ionization by changing the physical properties of the drug in different portions of the G.I tract, can lead to regional variability in absorption of drugs.

1.5.1.2. Physiological factors:

(a). Mechanism of absorption:

Perorally administered drugs are absorbed both by passive diffusion as well as by nonpassive means of absorption. Drugs absorbed by active and facilitated transport mechanisms show higher regional specificity due to the prevalence of these mechanisms only in a particular region of G.I tract.

(b). Metabolic Enzymes:

Presence of certain enzymes in a particular region of G.I tract can also lead to regional variability in absorption of drugs that are substrates to those enzymes. Intestinal metabolic enzymes principally, phase one metabolizers like cytochrome

P450 are abundantly present in the intestinal epithelium. Their activity decreases longitudinally along the small intestine, with the levels rising slightly from the duodenum to the jejunum and then declining in the ileum and colon. This non-uniform distribution of cytochrome P450 causes regional variability in the absorption of drugs that are substrate to these enzymes.

1.6: Gastric retention Systems:

Is a device, which resides in the confines of the stomach over a prolonged period of time (prolonging the residence time of the drug delivery system) for the purpose of providing a platform for controlled release of biologically active agents. The system releases the active agent to be absorbed or released from the stomach to be absorbed in the upper parts of the small intestine. In particular it allows for less frequent dosing of the active agent than with immediate release formulations or sustained released formulations that are not gastric retentive dosage forms. In other applications the frequency of dosing may be the same, but the gastric retention dosage forms will beneficially alter the absorption profile of the active agent from that available with immediate release formulations. This may result in increased bioavailability of the active agent with reduced side effects ²¹.

Over the last three decades, a various approaches have been pursued to prolong the residence time of a an oral dosage forms in the stomach, these methods include

- Floating systems ²²
- Swelling and expanding systems ^{23,24}
- Bioadhesive systems ^{25,26}
- Modified- shape systems ²⁷
- High density systems ^{28,29}
- Other gastric emptying devices ³⁰

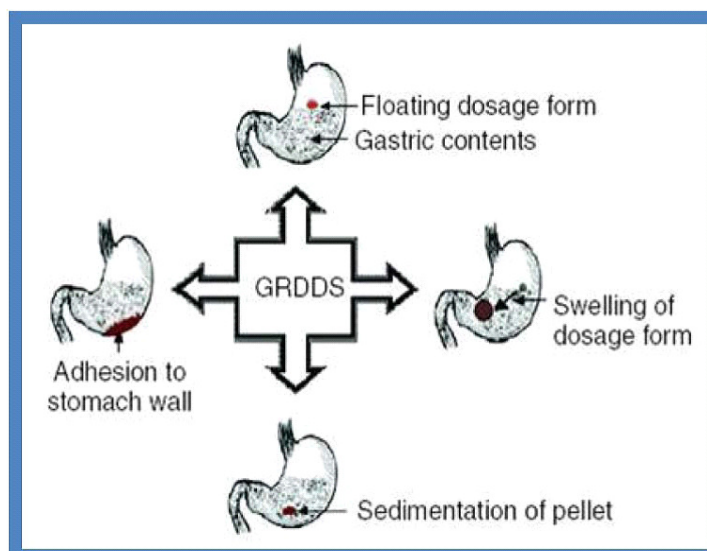


Fig.4. Different approaches of gastric retention

Peptic ulcer

A peptic ulcer, also known as PUD or peptic ulcer disease,^[1] is the most common ulcer of an area of the gastrointestinal tract that is usually acidic and thus extremely painful. It is defined as mucosal erosions equal to or greater than 0.5 cm. As many as 70–90% of such ulcers are associated with *Helicobacter pylori*, a spiral-shaped bacterium that lives in the acidic environment of the stomach; however, only 40% of those cases go to a doctor. Ulcers can also be caused or worsened by drugs such as aspirin, ibuprofen, and other NSAIDs.

Four times as many peptic ulcers arise in the duodenum—the first part of the small intestine, just after the stomach—as in the stomach itself. About 4% of gastric ulcers are caused by a malignant tumor, so multiple biopsies are needed to exclude cancer. Duodenal ulcers are generally benign.

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD), gastro-oesophageal reflux disease (GORD), gastric reflux disease, or acid reflux disease is a chronic symptom of mucosal damage caused by stomach acid coming up from the stomach into the esophagus.^[1] Informally called heartburn.

GERD is usually caused by changes in the barrier between the stomach and the esophagus, including abnormal relaxation of the lower esophageal sphincter, which normally holds the top of the stomach closed; impaired expulsion of gastric reflux from the esophagus, or hiatal hernia. These changes may be permanent or temporary ("transient").

Another kind of acid reflux, which causes respiratory and laryngeal signs and symptoms, is called laryngopharyngeal reflux (LPR) or "extraesophageal reflux disease" (EERD). Unlike GERD, LPR is unlikely to produce heartburn, and is sometimes called *silent reflux*.

REVIEW OF LITERATURE

Nicole M. *et al.*, (1991) studied the effect of simultaneous modification of medium composition and growth conditions on the production of *Lactococcus lactis* subsp. *cremoris* biomass in calcium alginate beads was studied by the response surface method. Statistical methods of data analysis for unbalanced experiments are illustrated. The media tested were whey, whey supplemented with yeast extract and/or meat extract, milk, and the commercial medium Gold Complete (Nordica). Fermentations were performed at 23°C under pH control (5.6, 6.0, 6.4, or 6.8). In one complete series, 1% CaCO₃ was added to the growth media. There were strong interactions between CaCO₃ and media, CaCO₃ and pH level, and CaCO₃, media, and pH level. In media with CaCO₃, all first-order interactions between media, pH, and sampling time were significant. The addition of CaCO₃ increased cell counts in whey-meat extract medium, but no significant difference was found with the other media. Uncoupling between growth and acidification occurred between 16 and 22 h. Highest counts were obtained on milk and Gold Complete (6 x 10¹⁰/g). In CaCO₃-containing media, pH influenced cell counts only in whey and in Gold Complete (pH 5.6 and 6.0 giving the best results); pH also influenced the bead mass obtained at the end of the fermentation. Biomass production in alginate gels is proposed as a method of obtaining concentrated cell suspensions without centrifugation or filtration.

Methal A. *et al.*, (2000) prepared anti-hapten IgG that was covalently immobilized on glutaraldehyde to prepared alginate-chitosan gel beads. The antibody immobilization efficiency was influenced by glutaraldehyde-bead reaction time, IgG concentration and pH. In addition, immobilization conditions such as glutaraldehyde and antibody concentrations influenced antibody hapten binding affinity. The immobilized IgG on the beads was stable and no reduction in the percent binding to hapten was noticed following 25 days of storage. It was concluded that antibodies could be successfully immobilized on alginate-chitosan gel beads. Such a system can be applied for the development of immunoaffinity purification and immunoassays.

Yoshifumi M. *et al.*, (2001) reported on preparation of Alginate gel beads were prepared which contained weak acid salts of chitosan (Alg-CS) and water-soluble vitamins (e.g. ascorbic acid (AS)) and the behavior of the beads, uptake of bile acids was investigated in vitro. The Alg-CS beads rapidly took up bile acid and this phenomenon was observed for both hydrogel beads and dried beads. About 120 mmol of taurocholic acid was taken up into Alg-CS (1 g) prepared with orotic acid. Dried Alg-CS is the granule which can be made easily, and keep chitosan-alginate multilayered beads for the ability of CS salt, and all elements can be taken as a food. Therefore, Alg-CS could serve as a useful dietary agent for the prevention of hyperlipidemia.

Ferreira P. *et al.*, (2002) studied that development of a new particulate drug delivery system using a sodium alginate matrix containing pindolol as a model drug molecule for intestinal drug prolonged release. Calcium alginate beads are known to be unable to control the release of most insoluble drugs. Pindolol-loaded alginate–gelatine beads have been developed using a solvent-free technique that involves a cross-linking reaction. Modifications in matrix structure and physicochemical behaviour caused by the cross-linking reaction were assessed during particle formation and drug release. Several parameters, such as matrix gelling rate, encapsulation efficiency, drug release profile and matrix erosion rate, were investigated. Physicochemical characterisation indicates the formation of a new alginate–gelatine matrix and shows that pindolol does not interfere with the matrix formation process. Matrix swelling of calcium alginate beads induced by phosphate buffer ends up in erosion and destruction. However, for cross-linked beads swelling does not lead to complete erosion, which may be the main cause of pindolol retention within the matrix. The modifications introduced in the initial calcium alginate formulation by means of an appropriate method such as the use of a cross-linking agent successfully changed the matrix performance, allowing the controlled release of pindolol.

Liuxing *et al.*, (2003) studied that the Colon-specific drug delivery systems (CDDSS) can be used to improve the bioavailability of protein and peptide drugs through the

oral route. A novel formulation for oral administration using coated calcium alginate gel beads-entrapped liposome and bee venom peptide as a model drug has been investigated for colon-specific drug delivery in vitro. Drug release studies under conditions mimicking stomach to colon transit have shown that the drug was protected from being released completely in the physiological environment of the stomach and small intestine. The release rate of bee venom from the coated calcium alginate gel beads-entrapped liposome was dependent on the concentration of calcium and sodium alginate, the amount of bee venom in the liposome, as well as the coating. Furthermore, a human g-scintigraphy technique was used in vivo to determine drug delivery more precisely. The colonic arrival time of the tablets was found to be 4–5 h. The results clearly demonstrated that the coated calcium alginate gel beads-entrapped liposome is a potential system for colon-specific drug delivery.

Wang S. *et al.*, (2004) prepared poly-*L*-arginine microbeads due to its nutritional function and pharmacological efficacy. A high-voltage electrostatic droplet generator was used to make uniform microcapsules. The results show that the membrane strength and permeating property are both remarkably affected with the changes of sodium alginate concentration. With the sodium alginate concentration increasing, gel beads sizes increase from 233µm to 350µm, release ratio is also higher at the same time, but the membrane strength decreases.

Patricio J. *et al.*, (2004) developed a new method of uptake of trivalent chromium by protonated dry alginate beads from aqueous solutions was investigated at 25 jC in batch-type experiments. The differences between the mechanisms associated with formation of alginate beads and with metal uptake were demonstrated. Uptake was coupled with a release of protons; this ion exchange was found to be the mechanism of the uptake. The uptake was strongly dependent on the Cr-bearing solution pH up to a value of around 4.5. Uptake reaches a value as high as 112 mg of chromium per g of alginate beads (dry wt.) at pH 4.5; this uptake is higher than that reported for several biosorbents. The experimental data fitted the Langmuir adsorption model; however, the maximum uptake computed from it was 32% lower than the value measured. SEM

analysis of the cross section of beads after uptake experiments showed no evidence of precipitation of chromium within the alginate beads at the pH ranges tested. A residual concentration around 0.3 mg/L of chromium, which allows safe discharge of solutions having Cr(III), was reached when alginate beads were challenged with a solution initially having as low as 10 mg/L of the metal. EPMA-EDX analysis of Cr-loaded beads showed a uniform distribution of chromic species throughout the structure of alginate beads, regardless of the solution pH.

Anal A. *et al.*, (2004) prepared chitosan-alginate multilayered beads for ampicillin and the The aim of this study is to develop multilayer beads with improved properties for controlled delivery of the antibiotic ampicillin. Ionotropic gelation was applied to prepare single and multilayer beads using various combinations of chitosan and Ca²⁺ as cationic components and alginate and polyphosphate as anions. Beads prepared with higher concentrations of chitosan entrapped more ampicillin. During incubation in simulated gastric fluid, the beads swelled and started to float but did not show any sign of erosion. Single layer chitosan–alginate beads released 70% of the drug within 4 h. Multilayer beads released only 20–30% in the same period of time. During subsequent incubation in simulated intestinal fluid, both single and multilayer beads continued to release drug. At least part of this release is due to disintegration of the beads. The rate of release both in gastric and intestinal fluid and the kinetics of disintegration in intestinal fluid can be controlled by changing the chitosan concentration in the coagulation fluid. The release of the drug can also be controlled by the degree of cross-linking using polyphosphate. Cross-linked multilayer beads were prepared that released only 40% of the entrapped drug during 24 h. It is concluded that chitosan–alginate multilayer beads, cross-linked with polyphosphate offer an opportunity for controlled gastrointestinal passage of compounds with low molecular weight like ampicillin.

Willem F. *et al.*, (2005) designed a Chitosan–alginate multilayer beads for controlled release of ampicillin, to develop multilayer beads with improved properties for controlled delivery of the antibiotic ampicillin. Ionotropic gelation was applied to

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Vani M. *et al.*, (2006) designed a gastro retentive floating beads of ranitidine hydrochloride were formulated to increase the residence time in stomach and to sustain the release behavior of the drug and increase drug bioavailability. The ranitidine hydrochloride floating beads were done by extrusion congealing method, because the major site of absorption of ranitidine hydrochloride is being the stomach, to extend the period of residence of the drug in the stomach to leave maximum absorption. Nine formulations of ranitidine hydrochloride floating beads were formulated by extrusion congealing technique using different percentage of gas forming agent and polymers, HPMC and sodium alginate. The content of drug release was done by UV spectrophotometer at 322 nm. The particle size analysis was done by

vernier calliper which was found to be in the range of 0.1-0.3. *In vitro* drug release of ranitidine hydrochloride, for F2 (3%w/w HPMC) and F6 (4%w/w HPMC) were found to be 80.12% and 81.10% respectively, at the end of 480 m in simulated gastric fluid (pH 1.2). The percentage drug entrapment and drug content of the formulated beads were found to be satisfactory by this method. From the study it was concluded that the gastro retentive drug delivery system designed as floating beads could be suitable drug delivery system for Ranitidine HCl. Further the *in vivo* absorption studies will confirm the suitability of the formulated dosage form.

George P. et al., (2006) prepared a method to investigate the swelling behavior and the *in vitro* release of the antihypertensive drug verapamil hydrochloride from calcium alginate and chitosan treated calcium alginate beads. Calcium–alginate beads, chitosan-coated alginate beads and alginate–chitosan mixed beads were synthesized and their morphology was investigated by scanning electron microscopy. The swelling ability of the beads in different media was found to be dependent on the presence of the polyelectrolyte complex between alginate and chitosan, the pH of the aqueous media and the initial physical state of the beads. The results revealed that the encapsulation of verapamil in both calcium–alginate and calcium alginate–chitosan mixed beads exceeded 80%. Considering the *in vitro* stability of verapamil encapsulating beads, 70% of the drug released from wet and dry plain calcium alginate beads within 1 and 3 h, respectively. The presence of chitosan was found to retard significantly the release from wet beads. However, in the case of dry beads the presence of chitosan had no significant effect on the initial release stage and significantly increased the release on the later stage. The results were analyzed by using a semi-empirical equation and it was found that the drug release mechanisms were either “anomalous transport” or “case-II transport”

Piyakulawat P. et al., (2006) studied that the hydrogel beads based on chitosan (CS) and carrageenan (CR) have been used as a controlled release device to deliver sodium diclofenac (DFNa) in the simulated gastrointestinal condition. Various factors potentially influencing the drug release (ie, CS/CR proportion, DFNa content, types

and amount of cross-linking agents) were also investigated. The optimal formulation was obtained with CS/CR proportion of 2/1 and 5%(wt/vol) DFNa. The controlled release of the drug from this formulation was superior to other formulations and was able to maintain the release for ~8 hours. Upon cross-linking with glutaric acid and glutaraldehyde, the resulting beads were found to be more efficient for prolonged drug release than their non-cross-linking counterparts. The bead cross-linked with glutaraldehyde was able to control the release of the drug over 24 hours. The difference in the drug release behaviour can be attributed to the differences in ionic interaction between the oppositely charged ions and to the concentrations of the drug within the beads, which depends on the compositions of the formulation and the pH of the dissolution medium. The release of drug was controlled by the mechanism of the dissolution of DFNa in the dissolution medium and the diffusion of DFNa through the hydrogel beads

Shishu S. *et al.*, (2006) developed a multiple-unit-type oral floating dosage form (FDF) of 5- fluorouracil (5-FU) to prolong gastric residence time, target stomach cancer, and increase drug bioavailability. The floating bead formulations were prepared by dispersing 5-FU together with calcium carbonate into a mixture of sodium alginate and hydroxypropyl methylcellulose solution and then dripping the dispersion into an acidified solution of calcium chloride. Calcium alginate beads were formed, as alginate undergoes ionotropic gelation by calcium ions and carbon dioxide develops from the reaction of carbonate salts with acid. The evolving gas permeated through the alginate matrix, leaving gas bubbles or pores, which provided the beads buoyancy. The prepared beads were evaluated for percent drug loading, drug entrapment efficiency, image, surface topography, buoyancy, and in vitro release. The formulations were optimized for different weight ratios of gas-forming agent and sodium alginate. The beads containing higher amounts of calcium carbonate demonstrated instantaneous, complete, and excellent floating ability over a period of 24 hours. The optimized formulation was subjected to in vivo antitumor studies to check the therapeutic efficacy of the floating dosage forms containing 5-FU against benzo(a)pyrene-induced stomach tumors in albino female mice (Balb/C strain). The multiple-bead FDF was found to reduce the tumor incidence in mice by 74%, while

the conventional tablet dosage form reduced this incidence by only 25%. Results indicate that FDF performed significantly better than the simple tablet dosage form.

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Khazaeli P. *et al.*, (2008) designed formulation of gel beads of Ibuprofen by ionotropic gelation method. Formulation of ibuprofen in beads could reduce its gastric ulcerogenicity. Alginate has a unique gel-forming property in the presence of multivalent cations, in an aqueous medium. Hence, in this study the formation of Ca-alginate ibuprofen beads, through ionotropic gelation has been investigated. For this purpose, different cross- linking agents including: Ca^{2+} , Ba^{2+} , Mn^{2+} , Co^{2+} , Sn^{2+} and Pb^{2+} , were used for bead preparation. Next, characterization of the beads, size

distribution, encapsulation efficiency of ibuprofen within the beads, the bead swelling and the drug release kinetic were investigated. Results showed that only Ca ion is suitable for the formation of ibuprofen beads. A good swelling profile for beads in phosphate buffer (pH=7.4) and the lack of swelling in hydrochloric acid (pH= 1.2), show the suitable nature of the beads. In addition, formulation of Na-alginate (2%) and Ca-chloride (2%) beads resulted in an encapsulation efficacy of around 90%. The drug release studies showed a rapid and complete ibuprofen release from the beads, especially those prepared from Na-alginate (2%) and Ca-chloride (2%), in phosphate buffer medium. However, no detectable drug release was observed within the acidic medium. In conclusion, ibuprofen is capable of being microencapsulated as a bead formulation, with suitable properties and release profile.

Mishra S. *et al.*, (2008) Formulated oil entrapped gastro retentive floating gel beads of loratadine. A gastro retentive controlled release system of loratadine was formulated to increase the residence time in stomach and to modulate the release behaviour of the drug. Oil entrapped floating microbeads prepared by the emulsion gelation method were optimized by 23 factorial design and a polymer ratio of 2.5:1.5 (pectin/sodium alginate) by mass, 15% (m/V) of oil (mineral oil or castor oil) and 0.45 mol L⁻¹ calcium chloride solution as the optimized processing conditions for the desired buoyancy and physical stability. *In vitro* drug release in the fed state conditions demonstrated sustained release of loratadine for 8 h, which best fitted the Peppas model with $n < 0.45$. The ethyl cellulose coating on microbeads optimized by factorial design resulted in a controlled release formulation of loratadine that provided zero-order release for 8 h.

Venkatesh D. *et al.*, (2008) developed a method to treat cough by preparing alginate beads of ambroxol Hydrochloride. Ambroxol, a mucolytic agent has been used for decades as a secretion releasing expectorant in the treatment of variety of respiratory disorders. This drug has a shorter half life 4 h₄ that requires frequent daily dosing and chronic respiratory diseases necessitates its formulation into a sustained release dosage form. Once or twice daily administration of controlled release preparations is

recommended and improves patient compliance. The major drawback of orally administered drug like ambroxol as mucolytic agent in a variety of respiratory disorders has a shorter biological half-life. To overcome these drawbacks, an attempt has been made to develop a sustained release dosage form of ambroxol embedded alginate microbeads prepared by ionotropic gelation technique. The beads were characterized for its particle size, drug content and *in vitro* release studies. The results revealed that the surface adhering drug was found to release immediately and a steady state of release was obtained up to 12 h from all the batches. The results indicated there was an inverse relationship between the concentration of alginate and drug release. The drug release was found to follow non-fickian diffusion obeying first order kinetics. These microbeads were characterized for its particle size, drug content and *in vitro* drug release studies. An attempt was also made to understand the mechanism involved in the release kinetics of alginate microbeads.

Gattani S. *et al.*, (2009) designed Floating-Muco adhesive Beads of Clarithromycin for the Treatment of *Helicobacter pylori* Infection. An excellent concept of floating system suffers from a disadvantage that it is effective only when the fluid level in stomach is sufficiently high; however, as the stomach empties and the tablet is at the pylorus, the buoyancy of the dosage form may be impeded. This serious limitation can be overcome by the use of bio-adhesive polymers to enable it to adhere to the mucous lining of stomach wall. Floating and bio-adhesive drug delivery systems offer the advantages of increased contact time with stomach mucosa, more effective absorption and bioavailability of drugs with absorption windows near proximal intestine and stomach, and low dosing frequencies. Our main aim of the present study was to develop alginate/hydroxypropyl methylcellulose (HPMC) based floating-mucoadhesive beads of clarithromycin to provide prolonged contact time of antibiotic to treat stomach ulcer. Floating-mucoadhesive beads were prepared and characterized for *in vitro* performance followed by investigation of *ex vivo* study in albino-wistar rats. Beads were prepared by ionic gelation technique where calcium chloride used as gelating agent and incorporated liquid paraffin for floating of the beads. Prepared beads were evaluated extensively for particle size, drug entrapment; swelling and surface morphology by using scanning electron microscopy. X-ray radioimaging

study in rabbits, *in vitro* mucoadhesion using rat stomach mucosal membrane and *in vitro* drug release studies were carried out. *Ex vivo* performance of alginate-HPMC beads were studied using albino rats in comparison to simple alginate-calcium beads. Alginate-HPMC beads may be suitable floating-muco-adhesive drug delivery system for delivering clarithromycin to treat stomach ulcers. Stomach-specific antibiotic drug delivery would be highly beneficial in the treatment of *H. pylori* infection in peptic ulcer disease.⁹) Clarithromycin is having good stability in a gastric pH.¹⁰) The present work describes incorporation of an active component known to be effective against *H. pylori*, clarithromycin, into alginate (Alg)-Ca and Alg-HPMC beads and reports the release of drug from the beads in an acidic environment and also applies the new approach of mucoadhesive and floating for synergistic effect.

Bindu B. et al., (2009) prepared an anti-depression therapy by formulating venlafaxine hcl enclosed in alginate microbeads prepared by iontophoretic gelation method. Venlafaxine hydrochloride (VEN) is a representative of a new class of antidepressants. VEN, commercially known as “Effexor” is a representative of a new class of antidepressants with a dose of 25mg-45mg. It acts by inhibiting selectively the uptake of serotonin and noradrenaline but shows no affinity for neurotransmitter receptors. Higher solubility in water results in burst effect with sudden peak levels of drug in blood. The half lives of VEN and its active metabolite O-desmethyl venlafaxine are 5hr and 11hr respectively. The micro beads were prepared by the ionotropic gelation of sodium alginate in calcium chloride solution. The prepared micro beads were evaluated mainly for the sustain release of the drug apart from the other tests like, % drug encapsulation, particle size and drug polymer compatibility by the FTIR studies. The method had resulted in good encapsulation efficiency and micron sized alginate spheres. The drug release was found to be sustained for 16 hours. Patients who experience intolerable nausea with an immediate-release formulation despite seeing improvement in their depressive symptoms might benefit from taking a controlled-release formulation of the same antidepressant or switching to another of the newer antidepressants. To reduce the adverse effects and to have the controlled release of the drug we have prepared the alginate micro beads of the drug.

Jaiswal D. *et al.*, (2009) studied formulation and evaluation of oil entrapped floating alginate beads of ranitidine hydrochloride . They develop a multi-unit gastro retentive sustained release dosage form of a water soluble drug, Ranitidine hydrochloride, from a completely aqueous environment avoiding the use of any organic solvent, which could cure peptic ulcer more efficiently by releasing the drug especially in stomach and also for a prolonged duration of time. A new emulsion gelation technique was used to prepare emulsion gel beads using sodium alginate as the polymer. The gel beads containing oil was prepared by gently mixing or homogenizing oil and water phase containing sodium alginate which was then extruded in to calcium chloride solution. The effects of factors like concentration of oil, curing time, drug: polymer ratio, alginate: pectin ratio and curing agent on drug entrapment efficiency, floating lag time, morphology and drug release were studied. Minimizing the curing time of beads leaded to enhanced drug entrapment efficiency. It was found that sodium alginate was not sufficient to sustain the drug release at gastric pH. Instead of it, appropriate combination of alginate and pectin could provide the sustain release of drug. The results show that these beads can entrap even a water soluble drug as Ranitidine hydrochloride in sufficient amount and also can successfully deliver the drug in stomach for a prolong duration of time without using any organic solvent and any time consuming step in the preparation.

Shaji S. *et al.*, (2009) prepared multi particulate gastro retentive dosage form of famotidine for better control of gastric acidity. The concept of multiunit gastro retentive beads can be utilized to provide a more reliable and long lasting release of drug in the stomach for local and systemic action. The floating gel beads beneficially alter the absorption of drug, thereby enhancing bioavailability. Famotidine, being a poorly bioavailable drug due to reasons unrelated to hepatic metabolism, is ideally suited to be delivered through a controlled release floating multiunit dosage form for slow release in the stomach and subsequent complete absorption in the intestine. Worldwide accepted clinical therapy of acid peptic disease is based on histamine H₂ receptor antagonists. The four H₂ receptor antagonists currently available on market are Cimetidine, Ranitidine, Famotidine, and Nizatidine. Out of these drugs famotidine is the most widely used and accepted drug for the treatment of peptic ulcer.

Famotidine is having fewer side effects than the other congeners and it does not appear to exhibit anti androgenic activity or affect the hepatic clearance of other drugs. Famotidine is having low bioavailability (40%), so there is a continued effort to improve the pharmaceutical formulation of famotidine in order to achieve an optimized therapy.

Salunke K. *et al.*, (2010) prepared a floating microcarriers of an antidiabetic drug Metformin hydrochloride is an Antihyperglycemic agent widely used in the management of NIDDM. Absolute oral bioavailability of Metformin hydrochloride is 50-60% due to its site-specific absorption limitations. It is safe drug and it has a half-life of 2 hrs. It is not absorbed completely and gives low bioavailability problem. Almost 80-100% of the drug is excreted unchanged. The total daily requirement of Metformin hydrochloride is 1.5-3g/day. Henceforth, there being high incidence of GI side effects and toxicity . Therefore, there are continued efforts to improve the pharmaceutical formulation of Metformin hydrochloride in order to achieve an optimal therapy. Bioavailability of the drug has been found to be reduced further with sustained release dosage forms, probably due to the fact that passage of the sustained release single unit dosage forms from absorption region of the drug is faster than its release and most of the drug released at the colon where Metformin hydrochloride is poorly absorbed . Floating microbeads were prepared from a sodium alginate solution containing CaCO_3 and NaHCO_3 as gas-forming agents. The solution was dropped to 5% CaCl_2 solution containing 10% acetic acid for CO_2 gas and gel formation. The effects of gas-forming agents on microcarrier size and floating ability were investigated. As concentration of gas-forming agents increased, the size and floating ability also increased. Microcarrier's surface and cross-sectional morphology were examined with Scanning Electron Microscopy. NaHCO_3 significantly increased porosity and pore diameter than CaCO_3 . Incorporation of CaCO_3 into alginate solution resulted in smoother microcarriers than those produced with NaHCO_3 as well as it showed high drug entrapment. Microcarriers incorporating CaCO_3 exhibited significantly increased gel strength over control and NaHCO_3 -containing samples. Release rate of Metformin hydrochloride increased proportionally with addition of NaHCO_3 . However, increasing weight ratios of CaCO_3 did not appreciably accelerate

drug release. The results of these studies indicate that CaCO_3 is superior to NaHCO_3 as an effervescent agent in alginate micro carrier's preparations. The enhanced buoyancy and sustained release properties of CaCO_3 -containing beads make them an excellent candidate for floating drug dosage systems

Yellanki S. et al., (2010) prepared a multiple unit type oral floating dosage form (FDF) of Riboflavin was developed to prolong gastric residence time, and increase drug bioavailability. The floating bead formulations were prepared by dispersing Riboflavin together with calcium carbonate into a mixture of sodium alginate and hydroxypropyl methylcellulose solution and then dripping the dispersion into an acidified solution of 1% (w/v) calcium chloride. The formulations were optimized for different weight ratios of gas forming agent and sodium alginate. Prepared

microbeads were evaluated for Particle size, Scanning electron microscopy, In-Vitro

buoyancy study, Drug entrapment efficiency and In Vitro drug release. The beads containing higher amounts of calcium carbonate demonstrated instantaneous, complete, and excellent floating ability. All the formulations remained buoyant and controlled release for up to 10 hrs. The mechanism of drug release was found to follow Higuchi matrix order release. Results indicate that FDF performed significantly better than the simple tablet dosage form. In context of the above principles, a strong need was recognized for the development of floating dosage form to deliver Riboflavin (model drug) in stomach to increase the efficiency of the drug, providing sustained release.

Tripathi G. et al., (2010) designed a buoyant beads of clarithromycin. They develop a consistent formulation of Cl that enjoys all the advantages of a floating single unit dosage form but at the same time being devoided of disadvantages of single unit dosage forms, like sticking or being obstructed in the gastrointestinal tract. Buoyant

beads of gellan was developed by inotropic gelation technique using calcium carbonate as gas forming agent and the drug polymer dispersion was emulsified with mineral oil. The oil was entrapped and blended with hydroxypropyl methyl cellulose or carbopol 934. The developed beads were evaluated in terms of diameter, % floating, encapsulation efficiency, In vitro drug release, In vivo gastric residence efficacy and clarithromycin concentration in the mucosa of the experimental animal model. The scanning electron microscope photograph indicated that the prepared beads were spherical in shape and buoyancy, encapsulation efficiency and drug content obtained from all batches were satisfactory. Particle size and percentage buoyancy of the gel beads increased by raising the concentration of calcium carbonate.

Goudanavar P. et al., (2010) prepared microbeads for Diclofenac sodium prepared by ionotropic gelation technique using Sodium alginate alone and combination with Hydroxypropyl methyl cellulose, Chitosan, Pectin as release rate modifiers, and investigated for flow behavior, particle size, swelling properties, surface study by SEM, and in vitro drug release potential. While increase in the concentration of sodium alginate and other polymer dispersions increased sphericity, size distribution, mean particle size. Drug entrapment efficiency approached nearly 95%. Increasing calcium chloride concentration decreases the mean diameter of the microbeads, no appreciable change in morphology, and drug release behaviors. In vitro drug release was dependent on the pH of the medium and concentration of polymer dispersions. Among the nine formulation batches F5, F7 and F9 were found to show optimum sustained effect. The mechanism of drug release from the microbeads was found to be followed super case-II transport.

Manjanna K. et al., (2010) Prepared Calcium alginate cross-linked polymeric microbeads of aceclofenac for oral sustained drug delivery in arthritis aceclofenac, a novel NSAID used in the treatment of rheumatoid arthritis, frequency of administration may cause certain GI-adverse effects. He develop a microparticulate oral sustained release dosage form, to reduce dosing frequency, to eliminate the dose related adverse effects and to ultimately improve compliance in the pharmacotherapy

of arthritis. The microbeads were prepared by an ionotropic external gelation technique, by using sodium alginate as the hydrophilic carrier and calcium chloride as the crosslinking agent. The mean particle sizes of drug-loaded microbeads were found to be in the range 596.45 ± 1.04 to 880.10 ± 0.13 μm . The drug entrapment efficiency was obtained in the range of 63.24-98.90% (w/v). The release of drug from the microbeads at pH 1.2 is negligible. Under neutral conditions, the beads will swell and the drug release on swelling and the erosion process resulting in an optimum level of drug released in a sustained manner which exhibits zero-order kinetics.

Kawadkar J. *et al.*, (2010) prepared Colonic drug delivery (CDD), Zn-pectinate gel (ZPG) microbeads of mesalazine is intended for the local treatment of ulcerative colitis, inflammatory bowel diseases and can potentially be used for colon cancer or the systemic administration of drugs that are adversely affected by the upper gastrointestinal (GI) tract. CDD have advantages of minimum systemic absorption, administration of lower drug doses, high concentrations of drug in the distal small intestine and the colon without systemic exposure and toxicity. There has been considerable investigation for the design of CDD systems and targeting has been achieved by different methods. Delivery systems controlling release of drug only in the colon has been reported. MZ ($t_{1/2}$: 0.6 to 1.4 hrs) is rapidly absorbed from the small intestine and there is a little localization in the colon relative to the small intestine. Therefore, to increase its localization in the colon; development of a polysaccharide based delivery system is required. The rationale for the development of a polysaccharide based delivery system for colon is the ability of the colonic microflora to degrade various types of polysaccharides that escape small bowel digestion. Major efforts have been focused should be deleted for pectin derivatives and use of calcium and zinc salts of pectin because binding of calcium and zinc induces non-covalent associations of carbohydrate chains through “eggbox” complexes, which are more water resistant, while still enzymatically degradable. In this study the effects of different formulation variables upon the characteristics of pectinate microbeads prepared by ionotropic gelation technique for colonic delivery of mesalazine was investigated.

Sangeetha S. et al., (2010) prepared Gastroretentive bead of theophylline by ionotropic gelation was formulated in two different combinations such as sodium alginate along with guar gum and sodium alginate with hydroxy ethyl cellulose. The gas forming agent's calcium carbonate was also added in four different concentrations. The formulated beads were then evaluated for particle size, drug content, floating properties and *invitro* dissolution. The *invitro* release study showed about 98-99% of drug release at the end of 8 hrs with good buoyancy effect for the batch formulated with the combination of sodium alginate and guar gum. The *invitro* release mechanism was found to be anomalous diffusion with first order kinetics .

Ahmed M. et al., (2010) designed an new oral drug delivery system was developed utilizing both the concepts of controlled release and mucoadhesiveness, in order to obtain a unique drug delivery system which could remain in stomach and control the drug release for longer period of time. Gastro-retentive beads of captopril were prepared by orifice ionic gelation method in 1:1 and 9:1 ratio of alginate along with mucoadhesive polymers viz; hydroxy propyl methyl cellulose, carbopol 934P, chitosan and cellulose acetate phthalate. The prepared beads were subjected for various evaluation parameters. The percentage drug content was found to be in the range of 59.4 - 91.9 percent for beads. It was observed that as the alginate proportion was increased, the average size of beads also increased. Photomicrographs revealed that the beads were spherical in shape. Alginate-chitosan (9:1) beads showed excellent microencapsulation efficiency (89.7 percent). Alginate- Carbopol 934P exhibited maximum efficiency of mucoadhesion in 0.1 N hydrochloric acid (44 percent for 1:1 and 22 percent for 9:1) at the end of 8 hours, whereas least mucoadhesion was observed with alginate-Cellulose acetate phthalate beads. The *in vitro* release studies were carried out in 0.1 N hydrochloric acid and the release were found to be more sustained with Alginate-chitosan beads (9:1) than Alginate-Carbopol 934P (1:1) beads. The alginate-cellulose acetate phthalate beads showed the better sustained release as compared to all other alginate-polymer combinations. Regression analysis showed that the release followed zero order kinetics in 0.1 N hydrochloric acid (pH 1.2). The objectives of the present work was achieved ie, formulation, evaluation and usefulness of sodium alginate mucoadhesive beads of captopril with different

mucoadhesive polymers. Certainly these findings can be applied for sustained delivery of drugs with mucoadhesion. Further these findings help the industry to scale up the commercial production

Sakthisaravanan V. *et al.*, (2010) studied on gastro retentive beads of theophylline by ionotropic gelation. There are various approaches which have been worked out to improve the retention of an oral dosage form in the stomach, e.g. floating systems,

swelling and expanding systems, modified- shape systems, bioadhesive systems, high

density systems and other delayed gastric emptying device. Floating drug delivery systems (FDDS) or hydro dynamically balanced systems (HBS) have a bulk density lower than gastric fluids and therefore remains floating in the stomach unflattering the gastric emptying rate for a prolonged period. This leads to an increase in the gastric retention time and a better control over fluctuations in plasma drug concentration. Sodium alginate and guar gum (hydrocolloids) were used to prepare beads as sodium alginate and guar gum is naturally occurring polymer widely used in various formulations and HEC a synthetic polymer. Hence based on all the discussion we have planned to investigate the feasibility of the formulations such as to prepare gastro retentive beads by ionotropic gelation with the help of sodium alginate with HEC and also sodium alginate with guar gum as two different formulations, to find out whether varying the concentrations of calcium carbonate express any substantial effect on the invitro release and floating ability for the formulated beads.

Table-2 : Various types of Gel Beads by using different Drugs and different Polymer.

Anti inflammatory drug					
Sl. No	Types	Drug	Polymer	Significance	Reference
1	Gel beads	Sodium diclofenac	Chitosan, carrageenan	<p>-Crosslinked beads with glutaric acid shows better result than non crosslinked.</p> <p>-Crosslinked beads with glutarelddehyde is best with regard to effectiveness for</p>	Pimwipha et.al.2007

				prolong drug release.	
2	Gel beads	Ibuprofen	Sodium alginate	-Calcium chloride is best, over BaCl_2 , MnCl_2 , CoCl_2 & SnCl_2	Khazaeli et.al.2008
3	Hydrophilic polymeric beads	Sodium diclofenac	Sodium alginate, sodium CMC	-Sodium CMC shows more prolonged drug delivery than sodium alginate.	Dhanaraju et.al.2010
4	Agarose beads	Aceclofenac	Sodium alginate	-Swelling index is increased and drug release rate is decreased with increasing polymer concentration.	Yesmin et.al.2008

SI. No	Types	Drug	Polymer	Significance	Reference
5	Microbeads	Ibuprofen	Sodium alginate	-Sweet potato flour is a potentially useful natural materials for making controlled release drug loaded microbead by ionotropic gelation method.	Jha et.al.2010
6	Microbeads	Diclofenac	Chitosan, HPMC	-Formulation with 1%HPMC&1%chitosan shows more sustained release than other.	Goudanavar et.al.2010
7	Gel beads	Ketoprofen	Sodium alginate	-As HPMC concentration increase,sustained release also increased.	Giunchedi et. al. 2004
8	Gel beads	Flurbi-profen	Cetylalcohol, ethyl alcohol	-Beads shows more sustained release upto 12 hrs. -Inherent strength of melt solidified bonds of drug helped to reduce the amount of excipient required to retard release.	Maheshwari et.al.2003

SI. No	Types	Drug	Polymer	Significance	Reference
9	Calcium pactinate beads	Aceclo-fenac	Low methoxy pectin, sodium alginate	-As sodium bi-carbonate concentration increased, floating ability of beads increased.-	Somani et.al.2010
Anti ulcer drug					
10	Floating beads	Ranitidine	Sodium alginate	%EE of beads prepared with two type of polymer(sod.alginate & pectine) is more than one type of polymer sodium alginate. -As Polymer concentration increased, swelling ratio decreased. -Oil act as a water barrier	Jaiswal et.al.2009
Anti biotics (beta lactamase)					
11	Multi layered beads	Ampicillin	Sodium alginate	-Chitosan beads more efficient than alginate beads. -Multilayered beads showed more delay in release of drug in chitosan-alginate beads	Anal et.al.2005

Anti microbials					
12	Polymer network beads	Ofo-floxacin	Chitosan, Sodium alginate	-Highest dissolution rate is observed with chitosan and sodium alginate and lowest with chitosan.	Kulkarni et.al.2010
13	Floating muco-adhesive beads	Clarithromycin	HPMC, Sodium alginate	-Alg.-calcium beads shows rapid release of drug within 3 to 5 hrs.	Gattani et. al.2010
Respiratory system					
14	GIT beads	Theophylline	Guar gum, Sodium alginate, Hydroxyl ethyl cellulose	-Theophylline release is faster from hydroxyl ethyl cellulose beads with alginate, when compared with guar gum-alginate. -On increasing conc, of CaCO ₃ , rate of release increased.	Sangeetha et.al .2010
15	PH dependent beads	Theophylline	Chitosan, sodium alginate	-Longer of cross linking time, lower the size of beads.	Khan et.al.2010
16	Alginate beads	Ambroxol	Sodium alginate	-It suggest that gel strength of alginate plays an IMP role in controlling drug release -Release rate of drug from beads decreased.	Venkatesh et.al.2008
17	Micro-beads	Theophylline	Chitosan, Sodium alginate	-As conc. Of polymer increased, size of beads also increased. -Lower cross linking time, lower the size Diameter of gel beads.	Sridhar et.al.2010

Vitamins					
18	Floating alginate beads	Riboflavin	Sodium alginate, HPMC	-Increased CaCO_3 conc.,prolongs the release of drug from beadsWithout CaCO_3 , formulation shows better release than gas forming agent.	Yellanki et.al.2010
19	Alginate beads	Water soluble vitamin. (bile acid)	Sodium alginate, Chitosan	-Alginate-Chitosan could potentially be useful for uptake of bile salts. - Alginate-Chitosan suitable for daily intake Orally administered,	Muratta et.al.2001
Proteins					
20	Chitosan-alginate beads	Lisinopril	Sodium alginate, Chitosan	-IgG antibodies has been covalently bound to Alginate-Chitosan beads using gluteraldehyde. -The successful immobilization of Ab on Alginate-Chitosan beads provides a good system for immunoaffinity purification&develop-ment of solid phase immunoassay	Albar-ghouthi et.al.2000

Anti-hypertensive					
Sl. No	Types	Drug	Polymer	Significance	Reference
21	Gellen beads	Hydrochlor thiazide	Gellen gum	<p>-Gellen hydrochlorthiazide beads system can be employed in anti-hypertensive treatment.</p> <p>-Also in patients requiring diuresis where sustain action of drug require.</p> <p>-Hydrochlorthiazide release from beads followed sustain action.</p>	Emeje et.al.2009
Anti ulcer drug					
22	Floating beads	5-fluorouracil	Sodium alginate, HPMC	<p>Results shows that release of drug from beads prolongs upto 24 hrs.</p> <p>-Delay in %drug release with increased In CaCO₃ concentration</p>	Gupta et.al.2007

Cholinergic drug					
Sl. No	Types	Drug	Polymer	Significance	Reference
23	Muco adhesive miocro beads	Timolol	Sodium alginate	<p>-Natural mucoadhesive system along with sodium alginate shows sustained and modulated in cointrolling release of timolol from microbeads.</p> <p>-Dissolution follows zero,first and higuchi model</p>	Sharma et.al.2009
Anti-histamine drug					
24	GIT floating beads	Loratadine	Low methoxy pectinate, Ethyl cellulose	<p>-Release rate follows zero order.</p> <p>-GIT formulation of drug having excellence buoyant ability and sustain drug release pattern could possibly advantageous in turns of increased bioavailability of drug.</p> <p>-GIT beads with mineral oils shows smaller diameter than castor oils.</p>	Mishra et.al 2008

Others					
Sl. No	Types	Drug	Polymer	Significance	Reference
25	Micro cannal bead	Iso-octane N-haxene	Gelatin	-Gelatin microbeads with narrow size distribution by using channel emulsification, a novel technology for preparing W/O or O/W emulsion. -Dried gelatin microbeads could be resuspended well in iso-octane	Lwamoto et.al.2001
Micro-organism					
26	Calcium Alginate beads	Lacto coccus lacti	Alginate	-Presence of CaCO ₃ helps in to maintain firmness of alginate beads despite increased production of lactic acid. -Highest yield were obtained in milk and gold,complet sustained with CaCO ₃ .	Morin et.al.1991
27	Gel beads	Tamarind gum	Sodium alginate	-Intresting for bio-medical application. -Gel beads are promising as a potentially good support to be employed in immobilization cell carrier terminology and fermentation industry with good economical feasibility and good quality.	Zhang et.al.2008

AIM AND PLAN OF WORK

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action. All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid, dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of an oral drug delivery systems¹⁵.

The basic rationale for controlled drug delivery is to alter pharmacokinetic and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration. These cover a wide range of prolonged action formulation which provide continuous release of their active ingredient at a pre-determined rate at predetermine time, reduced side effects, etc. Drug having a short elimination half-life, less frequent administration and better patient compliance may be obtained with sustained release preparation as compared to conventional dosage form.¹⁶

Sodium alginate beads are the one of the multiparticulate drug delivery system that are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability, and target to specific site. Sodium alginate will form reticulated structure with crosslinking agent like calcium ions or glutaraldehyde and this characteristic has been used to produce sustained release particulate systems for variety of drugs

The objective of the present study is to investigate the potential of gel beads of drug as long terms sustain release. Famotidine is a h₂ receptor antagonist; it is mainly used for the treatment of peptic ulcer. The successful treatment of peptic ulcer a depends on the maintenance of effective drug concentration level in the body for

which a constant and uniform supply of drug is desired. As its biological half-life is about 2 h and is eliminated rapidly, repeated daily administrations are needed to maintain effective plasma levels. It shows a low and irregular bioavailability of about 50% after oral administration with a high first pass effect. It has been suggested that drugs with biological half-lives in the range of 2–8 h are good candidates for sustained-release formulations. Sustained release dosage forms (gel beads) deliver the drug at a slow rate over an extended period of time and achieve this object.¹⁶

Sodium alginate Beads of famotidines will improve its bioavailability by bypassing the first pass metabolism because alginate beads shrink and unable to swell at acidic environment and the encapsulated drugs are not released where as they easily swell in an alkaline environment and release the drug.

A sustained-release formulation of famotidine is available in the market in various forms which include Coated granules, and matrix tablets, polyacrylate–polymethacrylate microspheres prepared by the solvent evaporation process, microcapsules and solid dispersions of famotidine in polyvinyl pyrrolidone (PVP)-microcrystalline cellulose and sustained-release tablets containing hydroxyl propyl methyl cellulose (HPMC) and cross-linked sodium carboxy methyl cellulose (CMC)¹⁶.

Though there are different varieties of controlled release formulations of famotidine is available in the market, there are no much controlled release capsules of famotidine. In this context the formulation of sodium alginate beads of Famotidine would be useful and it will be a potential carrier for the development of controlled release capsules which eventually will have the benefits such as reduction in dose, related side effects, improving the stability, bioavailability and patient compliance.

The technique adopted for the development of Famotidines microbeads could be applied for development of any other controlled release formulation using a newer drug candidate. In the proposed method inotropic gelation we drop the mixture of drug and polymer dispersion into aqueous calcium chloride solution, gelation occurs instantaneously resulting to the formation of spherical micro scale sized beads, with

narrow particle size, high yield, low porosity and optimum sustained release in various physiological gastrointestinal conditions.

Hence the present study was planned to develop and optimize sustained release oral product of Famotidine using sodium alginate beads as hydrophilic microbeads carrier. To optimize and control the release rate of drug from beads various release modifiers such as HPMC H4M, carbopol 71G, pectin and were used.

PLAN OF WORK

STAGE I

Preformulations

- Compatibility study: Compatibility of drug with various polymers by using IR.
- Preparation of standard calibration curve.

STAGE II FORMULATION OF SODIUM ALGinate MICRO BEADS BY IONOTROPIC GELATION METHOD

- General method of formulation
- Optimization of process variables for the formulation of sodium alginate microbeads Preparation.

a) Study on effect of different concentration of coating polymer on sodium alginate microbeads

a) HPMC (1,1.5,1.75 and2%)

b) Cabapol(1,1.5,1.75 and2%)

c) Pectin(1,1.5,1.75 and2%)

STAGE III

Evaluation of prepared placebo beads

- Percentage yield
- beads size Determination
- Swelling study

STAGE IV

Selection of optimized batches from various polymers using different ratios.

STAGE V

Preparation of drug loaded batches through optimized polymer ratio

1) Effect of various conc. of drug on optimized polymer ratio

5mg /500mg, 10mg/500mg, 20mg/500mg and 30mg/500mg.

STAGE VI

Evaluation parameters of drug loaded beads

- Drug content
- Encapsulation efficiency
- Loose surface crystal study
- Scanning electron microscopy
- *Invitro* release
- Release kinetics
- order of release
- mechanism of release

STAGE VII

Bioadhesion test of optimized batches.

STAGE VIII

Stability study of the optimized batches.

CHEMICALS AND MATERIALS USED

Table 6.1: Chemicals and materials used

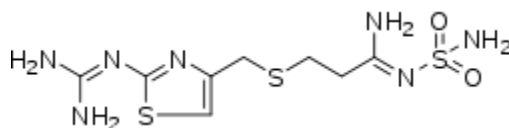
SI. No	Materials	Supplied by
1	Famotidine	Alkem pharmaceuticals Pvt Ltd, mumbai.
2	Sodium alginate	Nice chemicals, Banglore
3	Carbapol 71G	Yarrow chem Pdt Mumbai
4	Hydroxy propyl methyl cellulose K4M	High media laboratory Pvt ltd
5	Pectin	Nice chemicals, Banglore
6	Gelatin	Nice chemicals, Banglore
7	Glutaraldehyde	Nice chemicals, Banglore
	Calcium chloride	Nice chemicals, Banglore
8	Methanol	Nice chemicals, Banglore
9	Potassium bromide	
10	Potassium di hydrogen orthophosphate	Nice chemicals, Banglore
11	Sodium hydroxide	Nice chemicals, Banglore
12	Goat intestine	Slaughter house

INSTRUMENTS USED**Table 6.2: instruments used**

Sl.No	Instruments	Manufacturer
1	Electronic weighing Balance	Shimadzu BL220H ,Japan
2	Magnetic stirrer	Remiequipmentspvt limited
2	Hot Air Oven	Technico
3	Optical Microscope	Dolar US 4
4	UV-Spectroscopy	Shimadzu 1600, Japan
5	FTIR	Shimadzu 8400, Japan
7	Dissolution Test Apparatus	Electro Lab ,TDT 08L (USP)
9	Tablet disintegration apparatus	Rolet (IP/BP/USP)

Famotidine

Famotidine is a competitive, reversible inhibitor of the action of histamine at the histamine H₂-receptors, including receptors on the gastric cells. Famotidine does not lower serum Ca⁺⁺ in hypercalcemic states. Famotidine is not an anticholinergic agent.

Structure**Nomenclature:**

3-([2-(diaminomethyleneamino)thiazol-4-yl]methylthio)- N'-sulfamoylpropanimidamide

Molecular formula:

Molecular weight: 337.449 g/mol

Characters:

A white or pale yellow, crystalline powder, freely soluble in water and in methanol, sparingly soluble in ethanol, very slightly soluble in methylene chloride. It shows polymorphism.

Identification:

- Dissolve 10 mg in water and dilute to 100.0 ml with the same solvent. Dilute 5.0 ml of the solution to 50.0 ml with water. Examined between 220 nm and 360 nm, the solution shows two absorption maxima, at 229 nm and 315 nm. The ratio of the absorbance measured at the maximum at 229 nm to that measured at the maximum at 315 nm is 1.01 to 1.07.
- Examine by infrared absorption spectrophotometry, comparing with the spectrum obtained with ranitidine hydrochloride CRS. Examine the substances as mulls in liquid paraffin R. If the spectra show differences, dissolve 20 mg of the substance to be examined and 20 mg of the reference substance separately in 5 ml of methanol. Evaporate to dryness in a water-bath at 40°C under reduced pressure and with constant stirring. Dry the residues under high vacuum at 60°C for 1 h and record new spectra using the residues.

Tests:

Solution:

Dissolve 1.0 g in carbon dioxide-free water and dilute to 100.0 ml with the same solvent.

pH:

The pH of solution is 4.5 to 6.0.

Heavy metals:

1.0 g complies with limit test for heavy metals (20 ppm). Prepare the standard using 2 ml of lead standard solution (10 ppm Pb).

Loss on drying:

Not more than 0.75 per cent, determined on 1.000 g by drying under high vacuum at 60°C.

Sulphated ash:

Not more than 0.1 per cent, determined on 1.0 g.

Storage:

Store in an airtight container, protected from light.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

Absorption:

Famotidine is 50% absorbed after oral administration, compared to an intravenous (IV) injection with mean peak levels of 440 to 545 ng/ml occurring 2 to 3 hours after a 150-mg dose. Propantheline slightly delays and increases peak blood levels of Famotidine, probably by delaying gastric emptying and transit time. In one study, simultaneous administration of high-potency antacid (150 mmol) in fasting subjects has been reported to decrease the absorption of Famotidine .

Distribution:

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Metabolism:

In humans, the N-oxide is the principal metabolite in the urine; however, this amounts to <4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool. Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant, alterations in ranitidine half-life, distribution, clearance, and bioavailability.

Excretion:

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 ml/min, indicating active tubular excretion. The elimination half-life is 2.5 to 3 hours. Four patients with clinically significant renal function impairment (creatinine clearance 25 to 35 ml/min) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 ml/min, and a volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in proportion to creatinine clearance.

Pharmacodynamics:

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/ml. following a single oral dose of 150 mg, serum concentrations of Famotidine are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

Anti-secretary Activity

Effects on Acid Secretion:

Famotidine inhibits both daytime and nocturnal basal gastric acid secretions as well as gastric acid secretion stimulated by food, betazole, and pentagastrin. It appears that basal-, nocturnal-, and betazole-stimulated secretions are most sensitive to inhibition by Famotidine, responding almost completely to doses of 100 mg or less, while pentagastrin- and food-stimulated secretions are more difficult to suppress.

Effects on Other Gastrointestinal Secretions:

Oral Famotidine does not affect pepsin secretion. Total pepsin output is reduced in proportion to the decrease in volume of gastric juice. And it has no significant effect on pentagastrin-stimulated intrinsic factor secretion. Famotidine has little or no effect on fasting or postprandial serum gastrin.

Other Pharmacologic Actions

- 1) Prolactin levels-no effect in recommended oral or intravenous (IV) dosage, but small, transient, dose-related increases in serum prolactin have been reported after IV bolus injections of 100 mg or more.
- 2) Other pituitary hormones-no effect on serum gonadotropins, TSH, or GH. Possible impairment of vasopressin release. No change in cortisol, aldosterone, androgen, or estrogen levels. No antiandrogenic action.
- 3) No effect on count, motility, or morphology of sperm.

Side Effects

The following have been reported as events in clinical trials or in the routine management of patients treated with Famotidine . The relationship to therapy with Famotidine has been unclear in many cases. Headache, sometimes severe, seems to be related to administration of Famotidine . Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats. Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis. Rash, including rare cases of erythema multiforme. Rare cases of alopecia and vasculitis. Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

Drug Interactions

Although Famotidine has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450 linked oxygenase enzymes in the liver. Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. In a ranitidine-triazolam drug-drug interaction study, triazolam plasma concentrations were higher during b.i.d. dosing of ranitidine than triazolam given alone.

Precautions:

General

1. Symptomatic response to therapy with Famotidine does not preclude the presence of gastric malignancy.
2. Since Famotidine is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function. Caution should be observed in patients with hepatic dysfunction since Famotidine is metabolized in the liver.
3. Rare reports suggest that Famotidine may precipitate acute porphyric attacks in patients with acute porphyria. It should therefore be avoided in patients with a history of acute porphyria.
4. Pregnancy Category B. This drug should be used during pregnancy only if clearly needed.

Famotidine is secreted in human milk. Caution should be exercised when it is administered to a nursing mother.

5. The safety and effectiveness of Famotidine have been established in the age group of 1 month to 16 years for the treatment of duodenal and gastric ulcers, gastroesophageal reflux disease and erosive esophagitis, and the maintenance of healed duodenal and gastric ulcer. Safety and effectiveness in neonates (less than 1 month of age) have not been established.

Overdose

There has been limited experience with over dosage. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience. In addition; abnormalities of gait and hypotension have been reported.

METHODOLOGY

STAGE I: PREFORMULATION STUDIES:

i. a) Physical Drug Excipient Compatibility Studies:

In designing a solid dosage form it is necessary to know the inherent stability of the drug substance and possibility of interaction with excipients. The physical compatibility studies were coupled with the stability studies at higher temperature and humidity conditions. The drug excipient compatibility study protocol includes the preparation of homogenous physical mixture in 1:1 ratio of drug and all possible excipients to be used in the formulation. The physical mixtures were sealed into 15ml USP type III flint glass vials and stored in humidity chamber for 30 days at 40°C temperature and 75% relative humidity conditions. The initial state of the mixtures was noted and further evaluation for the possible occurrence of any interactions was performed after the 15th and 30th day.

b) Infrared spectroscopy:

Drug excipient compatibility can alter the physicochemical property and bioavailability of the drug. This incompatibility thereby affects its safety and efficacy. Study of drug excipient compatibility is an important process in the development of the stable dosage form and it helps in the selection of right excipients. This increases the probability of developing a stable dosage form.

Infra-red spectroscopy can be used to investigate and predict any physicochemical interaction between different components in formulation and to determine the nature and extent of interaction. Therefore, it can be applied to the selection of suitable, chemically compatible excipients.

The aim of the present study was to find out the possible interaction between the selected polymers like sodium alginate, HPMC, chitosan, gelatin and pectin and the drug famotidine and also to identify the compatibility between the drug and the polymers.

1:100 ratios of sample and potassium bromide were taken in a mortar and triturated. A small amount of triturated sample was taken into a pellet maker and was compressed at 10kg/cm² using a hydraulic press. The pellet was kept on to the sample

holder and scanned from 4000cm⁻¹ to 400 cm⁻¹ in Shimadzu FTIR spectrophotometer. Samples were prepared for pure drug, pure polymer, and physical mixture of drug and polymer. The spectra obtained through those samples were compared and interpreted for the shifting of functional peaks.

- **Preparation of calibration curve**

Accurately weighed 100 mg of famotidine and was dissolved in minimum quantity of methanol and phosphate buffer mixture(2:1 ratio) in a 100ml volumetric flask and make up to 100 ml with phosphate buffer pH 6.8 to get the concentration of 1mg/ ml.(stock I).This stock solution was further diluted to get a concentration of 100µg/ml(stock II).Sock II solution was further diluted to get a series of concentration 1-10 µg/ml. absorbance of these solution measured at 235nm in uv spectrophotometer by taking 6.8 pH phosphate buffer as blank. Graph was plotted concentration Vs absorbance to obtain the standard calibration curve.²¹

STAGE II: FORMULATION OF SODIUM ALGINATE PLACEBO MICRO BEADS BY IONOTROPIC GELATION AND CROSS LINKING METHOD.

- **GENERAL METHOD OF FORMULATION OF SODIUM ALGINATE MICRO BEADS.**

Prepared 25ml of 2% solution of sodium alginate with distilled water by stirred it with mechanical stirrer. Added this dispersion by using syringe slowly in to a beaker containing 50ml of 2% solution of calcium chloride which was kept under continuous agitation at 100 rpm .Allowed the beads to be formed by running the stirrer 15 min checked the beads under microscope. Then rigidized the beads by adding 1ml of 25% solution of glutaraldehyde. Allowed the stirring for further 1 hour at 100 rpm. After stirring for one hour filtered the solution and collected the beads. Obtained micro beads were washed with water and dried at 50°C in an oven for 1 hour.

Formulation Batches :

Ingredients	Formulation code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Famotidine	10 (mg)	20 (mg)	30 (mg)	40 (mg)	10 (mg)	20 (mg)	30 (mg)	40 (mg)	10 (mg)	20 (mg)	30 (mg)	40 (mg)
Sodium alginate	0.2 (mg)	0.3 5 (mg)	0.4 5 (mg)	0.4 (mg)	0.2 (mg)	0.3 5 (mg)	0.4 5 (mg)	0.4 (mg)	0.2 (mg)	0.3 5 (mg)	0.4 5 (mg)	0.4 (mg)
Calcium chloride	0.2 mg	0.2 mg	0.2 mg	0.2 mg	0.2 mg	0.2 mg	0.2 mg	0.2 mg	0.2 mg	0.2 mg	0.2 mg	0.2 Mg
HPMC K4M	0.1 mg	0.3 Mg	0.6 mg	1 mg	-	-	-	-	-	-	-	-
Carbapol 71G	-	-	-	-	0.1 mg	0.3 Mg	0.6 mg	1 mg	-	-	-	-
Pectin	-	-	-	-	-	-	-	-	0.1 mg	0.3 Mg	0.6 mg	1 mg

- **OPTIMIZATION OF PROCESS VARIABLES FOR FORMULATIONS OF PLACEBO BEADS**
- **Study on effect of different concentration of HPMC K4M as release modifier on sodium alginate microbeads:**

Four batches of placebo microbeads were prepared by using sodium alginate and HPMC as coating polymer. To 25 ml of deionized water, 1% sodium alginate was added and stirred with magnetic stirrer then add 1% HPMC K4M to form uniform dispersion. The resulting dispersion was dropped through syringe with needle slowly into a beaker containing 50 ml of 2% aqueous solution of calcium chloride which is kept under continuous agitation at a slow speed using a magnetic stirrer. Allow the beads to be formed by running the stirrer 15 min. Checked the beads under microscope. Then rigidized the beads by adding 1ml of 25% solution of glutaraldehyde. Allow the stirring for further 1 hour 100 rpm. After stirring for one hour filtered the solution and collected the beads and dried it an oven and it was coded as **H₁**. By following above mentioned procedure three other batches were prepared and were coded as **H₂**, **H₃** and **H₄** respectively. All other variables were kept constant.

Table 6.4: composition of placebo beads of sodium alginate coated with HPMC as release modifier.

Formulation code	Sodium alginate	HPMC
H ₁	2.0%	1%
H ₂	1.75%	1.5%
H ₃	1.5%	2.0%
H ₄	1%	2.5%

- **Study on effect of different concentration of Carbopol 71 g release modifier on sodium alginate microbeads:**

Four batches of placebo microbeads were prepared by using sodium alginate and Carbopol 71 g as coating polymer. To 25 ml of deionized water, 1% sodium alginate was added and stirred with magnetic stirrer o form uniform dispersion .The resulting dispersion was dropped through syringe with needle slowly into a beaker containing1% Carbopol 71 g solution added 50 ml of 2% aqueous solution of calcium chloride which is kept under continuous agitation at a slow speed using a magnetic stirrer. Allow the beads to be formed by running the stirrer 15 min. Checked the beads under microscope. Then rigidized the beads by addition of 1ml of 25% solution of glutaraldehyde. Allowed the stirring for further 1 hour at 100 rpm. After stirring for one

hour filtered the solution and collected the beads and dried it an oven and it was coded as **C₁**. By following above mentioned procedure three other batches were prepared were different and coded as **C₂** ,**C₃** and **C₄** respectively. All other variables were kept constant.

Table 6.5: composition of placebo beads of sodium alginate coated with Carbopol G as release modifier.

Formulation code	Sodium alginate	Carbopol G
C₁	2.0%	1%
C₂	1.75%	1.5%
C₃	1.5%	2.0%
C₄	1%	2.5%

- **Study on effect of different concentration of pectin as release modifier on sodium alginate microbeads:**

Four batches of placebo microbeads were prepared by using sodium alginate and pectin as coating polymer. To 25 ml of deionized water, 1% sodium alginate was added and stirred with magnetic stirrer then add 1% Pectin to form uniform dispersion .The resulting dispersion was dropped through syringe with needle slowly into a beaker containing 50 ml of 2% aqueous solution of calcium chloride which is kept under continuous agitation at a slow speed using a magnetic stirrer. Allowed the beads to be formed by running the stirrer 15 min. Checked the beads under microscope. Then rigidized the beads by adding 1ml of 25% solution of glutaraldehyde. Allow the stirring for further 1 hour 100 rpm. After stirring for one hour filtered the solution and collected the beads and dried it an oven and it was coded as **P₁**. By following above mentioned procedure three other batches were prepared and were coded as **P₂**, **P₃** and **P₄** respectively. All other variables were kept constant

Table 6.6: composition of placebo beads of sodium alginate coated with Pectin as release modifier.

Formulation code	Sodium alginate	Pectin
P ₁	2.0%	1%
P ₂	1.75%	1.5%
P ₃	1.5%	2.0%
P ₄	1%	2.5%

STAGE III: EVALUATIONS OF PREPARED PLACEBO BEADS.**• Yield of production**

The yields of production of micro beads of various batches were calculated using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for preparation of microbeads and percent production yields were calculated as per the Formula mentioned below.²²

$$\text{Percentage yield} = (\text{practical yield/theoretical yield}) \times 100$$

• Measurement of bead size

This is determined by optical microscopy with the use of a calibrated eye piece micrometer.

• Determination of calibration factor of stage micrometer:

For determining calibration factor 4th division of stage micrometer was coincided with 7th division of eye piece micrometer (one smaller division of stage micrometer is equivalent to 10 micrometer)

ii) Determination of particle size and particle size distribution by optical microscope

The particle size and particle size distribution of microbeads were evaluated using optical microscope. The dried microbeads were spread on a clean and dried glass slide and examined on an optical microscope and size of the microbeads was measured by using the pre- calibrated ocular micrometer and stage micro meter. About 25 particles of each formulation were observed and counted.

Mean diameter of particle size microbeads was determined by using following formula.

Mean size= ($\Sigma nx / \Sigma n \times$ magnification value

Σnx =total number of beads \times mid-point of the size range

Σn = total number of beads.

- **Evaluation of swelling behaviour**

Swelling behaviour was studied by measuring the percentage water uptake by the beads. About 50 mg of beads were accurately weighed and placed in 100 ml of phosphate buffer (pH 6.8 and 0.1 N HCl (pH 1.2)). Beads were removed from their respective swelling media after 8 h and weighed after drying the surface water using filter paper. The water uptake was calculated as the ratio of the increase in weight of beads after swelling to the dry weight²³.

STAGE IV: SELECTION OF OPTIMIZED VARIABLES FROM THE PLACEBO BEADS.

Based on the physicochemical parameters of the placebo beads (high percentage yield, least size of the beads, high swelling index and lowest drying rate) the batches H₁, C₁ & P₁.

STAGE V: OPTIMIZATION OF PROCESS VARIABLE FOR FORMULATION OF DRUG LOADED BEADS.

- **Study on effect of various concentration of drug (famotidine) on HPMC K4M coated sodium alginate micro beads:**

Accurately weighed quantity of famotidine such as 10 mg was added to the selected batch of HPMC K4M coated microbeads such as H₁. The resulting dispersion was dropped through syringe with needle slowly into a beaker containing 50 ml of 2% aqueous solution of calcium chloride which is kept under continuous agitation at a slow speed using a magnetic stirrer. Allowed the beads to be formed by running the stirrer 15 min. checked the beads under microscope. Then rigidized the beads by adding 1ml of 25% solution of glutaraldehyde. Allowed the stirring for further 1 hour at 100 rpm. After stirring for one hour filtered the solution and collected the beads and dried it in an oven and it was coded as FH₁.

Similarly three other batches were prepared where; only the quantity of Famotidine added was different such as 20mg, 30mg, and 40mg. The concentration of

polymer was kept constant in all the batches such as 2.0% of sodium alginate and 1.0% of HPMC K4M and they were coded as **FH₂**, **FH₃** and **FH₄** respectively.

Table 6.8: composition of Famotidine loaded sodium alginate beads coated with HPMC K4M as release modifier.

Formulation code	Drug in mg/ 500 mg of Polymer	Batch selected with HPMC as release modifier
FH ₁	10	H ₁
FH ₂	20	H ₁
FH ₃	30	H ₁
FH ₄	40	H ₁

• **Study on effect of various concentration of drug (famotidine) on carbopol 71 G coated sodium alginate micro beads:**

Accurately weighed quantity of famotidine 5mg was added to the selected batch of Carbopol 71 G coated microbeads such as C₄. The resulting dispersion was dropped through syringe with needle slowly into a beaker containing 50 ml of 2% aqueous solution of calcium chloride containing carbopol 71 G solution which is kept under continuous agitation at a slow speed using a magnetic stirrer. Allow the beads to be formed by running the stirrer 15 min. Checked the beads under microscope. Then rigidized the beads by adding 1ml of 25% solution of glutaraldehyde. Allow the stirring for further 1 hour 100 rpm. After stirring for one hour filtered the solution and collected the beads and dried it in an oven and it was coded as FC₁.

Similarly three other batches were prepared where, only the quantity of Famotidine added was different such as 10mg, 20mg, and 30mg. The concentration of polymer was kept constant in all the batches such as 2% of sodium alginate and 1.0 % of Carbopol 71 G and they were coded as FC₂, FC₃ and FC₃ respectively. Table 6.4: composition of placebo beads of sodium alginate coated with HPMC as release modifier.

Table 6.9: composition of famotidine loaded sodium alginate beads coated with Carbopol 71 Gas release modifier.

Formulation code	Drug in mg/500 mg of polymer	Batch selected with Carbopol 71 Gas release modifier
FC ₁	10	C ₁
FC ₂	20	C ₁
FC ₃	30	C ₁
FC ₃	40	C ₁

- **Study on effect of various concentration of drug (famotidine) on pectin coated sodium alginate micro beads:**

Accurately weighed quantity of Famotidine 10 mg was added to the selected batch of Pectin coated microbeads such as FP₁. The resulting dispersion was dropped through syringe with needle slowly into a beaker containing 50 ml of 2% aqueous solution of calcium chloride which is kept under continuous agitation at a slow speed using a magnetic stirrer. Allow the beads to be formed by running the stirrer 15 min. Check the beads under microscope. Then rigidized the beads by adding 1ml of 25% solution of glutaraldehyde. Allow the stirring for further 1 hour 100 rpm. After stirring for one hour filtered the solution and collected the beads and dried it in an oven and it was coded as FP₁.

Similarly three other batches were prepared where, only the quantity of Famotidine added was different such as 10mg, 20mg, and 30mg. The concentration of polymer was kept constant in all the batches such as 2.0 % of sodium alginate and 1.0 % of Pectin and they were coded as **FP₂**, **FP₃** and **FP₄** respectively.

Table 6.10: composition of Famotidine loaded sodium alginate beads coated with Pectin as release modifier.

Formulation code	Drug in mg/500mg of polymer	Batch selected with Pectin as release modifier
FP ₁	10	P ₁
F _{P2}	20	P ₁
F _{P3}	30	P ₁
F _{P4}	40	P ₁

STAGE VI: EVALUATION PARAMETERS OF DRUG LOADED BEADS

- **Estimation of drug content²⁴**

Famotidine content in the microbeads was estimated by a UV-spectrophotometric method. Accurately weighed 50mg of microbeads were suspended in 100ml of phosphate buffer pH 6.8. The resulting solution was kept for 24hrs. Next day it was stirred for 15min. The solution was filtered, after suitable dilution, Famotidine content in the filtrate was analyzed at 235nm using Shimadzu 1201 UV-Visible spectrophotometer. The obtained absorbance was plotted on the standard curve to get the exact concentration of the drug. Calculating this concentration with dilution factor we got the percentage of actual drug content.

Estimation of encapsulation efficiency²⁵

Drug entrapment efficiency of Famotidine microbeads was performed by accurately weighing 50mg of microbeads and suspended in 100 ml of phosphate buffer pH6.8 and it was kept on a side for 24 hours. Then, it was stirred for 15 mins and filtered. After suitable dilution, Famotidine content in the filtrate was analyzed Spectrophotometrically at 235 nm using shimadzu 1201 U.V. Spectrophotometer. The obtained absorbance was plotted on the standard curve to get the exact concentration of the entrapped drug. Calculating this concentration with dilution factor we got the percentage of actual drug encapsulated in microbeads. The drug entrapment efficiency was determined using following relationship.

$$\% \text{ Drug entrapment efficiency} = \frac{\text{Actual drug content} \times 100}{\text{Theoretical drug content}}$$

- **Loose surface crystal study (LSC)²⁴**

This study was conducted to estimate the amount of drug present on the surface of the microbeads which showed immediate release in dissolution media. 100mg of microbeads were suspended in 100ml of phosphate buffer (pH 6.8), simulating the dissolution media. The Samples were shaken vigorously for 15min in a mechanical shaker. The amount of drug leached out from the surface was analyzed spectrophotometrically at 235nm. Percentage of drug released with respect to entrapped drug in the sample was recorded.

- **Scanning electron microscopy analysis (SEM)²⁶**

The shape and surface characteristics were determined by scanning electron microscopy (model-JSM, 35CF, jeol, Japan) using gold sputter technique. The particles were vacuum dried, coated to 200 Å thicknesses with gold palladium using prior to microscopy. A working distance of 20nm, a tilt of zero-degree and accelerating voltage of 15kv were the operating parameters. Photographs were taken within a range of 50-500 magnifications.

- **In-vitro release studies²⁷**

In-vitro release studies of prepared microbeads were carried out using phosphate buffer (pH 6.8) using USP- basket type apparatus. Accurately weighed quantity of 250 mg of prepared microbeads put into the basket rotated at a constant speed at 100rpm and maintained temperature $37 \pm 5^\circ\text{C}$ in 900ml of the dissolution medium (phosphate buffer H6.8). The sample was withdrawn at 0.5hrs, 1hrs, 2hrs, 3hrs, 4hrs, 5hrs, 6hrs, 7hrs, 8hrs, 9hrs, 10hrs, 11hrs, 12hrs, 14hrs, 18hrs, and 24hrs. Each time interval 5 ml of sample was withdrawn, at the same time 5 ml of fresh dissolution media was added to maintain sink condition. The withdrawn samples were suitably diluted and measured the absorbance at 235 nm Spectrophotometrically. Then calculated the cumulative percentage drug release at regular time intervals.

STAGE VII: IN VITRO RELEASE KINETIC STUDY ON SELECTED BATCHES OF FAMOTIDINE BEADS.

i) Determination of order of release of drug (Famotidine) from micro beads by graphical method.

To determine the order of release of drug from micro beads by graphical method from the dissolution data, a graph was plotted with % drug remaining Vs time. Zero order release can be confirmed if straight or linearity is obtained. To find out the release rate constant, the slope of the curve was found out and multiplied with 2.303. Regression coefficient of the curve was determined to confirm the correlation between X and Y axis.

In the second stage, using the same dissolution data, a graph was plotted with log% remaining Vs time. If a straight line or linearity is observed, it can be confirmed that the drug release follow first order kinetics. The slope of the graph was found out and multiplied with 2.303 to obtain the first order rate constant k_1 . Regression coefficient of the graph was found out to confirm the correlation between X and Y axis.

- **Study on mechanism of drug release**

In order to predict and correlate the release behavior of drug from the polymeric matrix, it is necessary to fit the *invitro* release data in to a suitable model. Hence the dissolution data were fitted according to the well-known exponential equation, which is often used to describe the drug release behavior from a polymer system. The equation which is used to describe drug release mechanism is:

$$M_t / M_\infty = kt^n$$

Where, M_t / M_∞ is the fraction release of the drugs' is the release time, 'k' is the constant, which indicate the properties of the macromolecular polymeric system, and 'n' is the release exponent indicative of the mechanism of release. The 'n' value was used for the analysis of drug release mechanism from drug loaded micro beads. The 'n' values were determined for all batches of drug loaded micro beads by graphical method, which is explained below.

In the first stage, a graph plotted with log% release Vs log time. If a straight line is obtained, then the regression coefficient was found out to confirm the linearity between X and Y. The slope (n) of the line was found out and if

-
- | | | |
|---------------------|---|---|
| $n \leq 0.5$ | : | The release is by Fickian diffusion |
| $n > 0.5$ and < 1 | : | The release mechanism is swelling |
| $n = 1$ | : | Release is by case II transport release mechanism |
| $n > 1$ | : | Release is by Super case II Transport |

In the second stage, a graph was plotted with % release Vs $\sqrt{\text{time}}$. If linearity is observed, the release mechanism is by Higuchi's diffusion.

STAGE IX: STABILITY STUDIES FOR BEST FORMULATION ²⁴

To assess the long term physical stability, micro beads from selected batches (FH₃ and FC₃) were filled into a hard gelatin capsules manually and wrapped the filled capsule with aluminum foil, and put this entire packet in to self-sealing polyethylene cover. The studies were performed at room temperature for period of 45 days. Change in Particle size distribution with optical microscope and change in drug content by Spectrophotometrically at 235 nm was calculated every 7 days for the entire period of stability study.

STAGE I

PRE-FORMULATION STUDIES:

Infrared spectroscopy

The compatibility of the drug and formulation is an important pre-requisite for formulation. An IR spectroscopic analysis was carried out to check the compatibility between the polymers and selected drug FAMOTIDINE. IR spectrum was obtained through pure polymer, pure drug, and drug- polymer physical mixture. These entire spectra were checked for shifting for major functional peaks and also they were observed for the appearance of new characteristic peaks.

The IR spectrum of FAMOTIDINE showed the peaks 35051.69 cm^{-1} (N-H stretching, amides), 3376.67 cm^{-1} (N-H asymmetric, sulphonamide), 3103.86 cm^{-1} (C-H stretch), 1331.03 cm^{-1} (Asymmetrical SO_2 stretching), 1171.3 cm^{-1} (symmetrical SO_2 stretching) and 902.07 cm^{-1} S-N stretching. These peaks can be considered as characteristic peaks of FAMOTIDINE and were not affected and prominently observed in IR spectra of FAMOTIDINE along with polymers as shown in Fig.1- Fig10. The spectra indicated no interaction between FAMOTIDINE and polymers.

IR spectrum of sodium alginate showed the characteristic peaks at 3176.76 cm^{-1} (OH- stretching) 1596 and 1407 cm^{-1} (COO- asymmetric and symmetric stretching), $1081\text{-}1024\text{ cm}^{-1}$ (C-O-C anti symmetric stretching), and carboxyl and carboxylate at about 1000 to 1400 cm^{-1} . These peaks can be considered as characteristic peaks of sodium alginate.

Infrared absorption spectrum of HPMC K4M (figure 7.3) shows all prominent 7 peaks. IR spectrum indicated characteristics peaks belonging to measure functional groups such as principal peaks at wave numbers 2922.59 , 3420.14 , 1058.73 , 1640.16 cm^{-1} . The major IR peaks observed in HPMC were 2922.59 ($2850 - 3000$) (C-H), 3420.14 ($3300 - 3500$) (NH), 1058.73 ($1000 - 1300$) (C-O) cm^{-1} .

An IR spectrum of Carbopol 71 G the peak at 3458.37 cm^{-1} corresponds to stretching vibrations of hydroxyl group in Carbopol 71 G. The backbone of the polymer is manifested through peak at 2925 cm^{-1} C-H aliphatic stretching vibrations.

The stretching vibrations of C O are found at 1716 cm^{-1} . Also C-H bending (CH_2) at 1450.47 cm^{-1} can also be observed.

FTIR spectra of pectin samples showed characteristic peaks at 3388.93, 2895.0, 1747.0 and 1053.13 cm^{-1} corresponding, respectively, to $-\text{OH}$, $-\text{CH}$, C O of ester and acid, and $-\text{COC}-$ stretching of the galactouronic acid.

The presence of same peak which are characteristic functional group of the FAMOTIDINE and polymers like sodium alginate, HPMC, Carbopol 71 G and Pectin are present in the drug polymer physical mixture confirm that there is no major shifting in the functional peak and there is no appearance of new characteristic peaks. There is no interaction between drug FAMOTIDINE and polymers like sodium alginate, HPMC, Carbopol 71 G and Pectin. Hence the selected drug FAMOTIDINE is found to be compatible with the selected polymers like sodium alginate, HPMC, Carbopol 71 G and Pectin.

Figure 7.1 IR spectrum of FAMOTIDINE

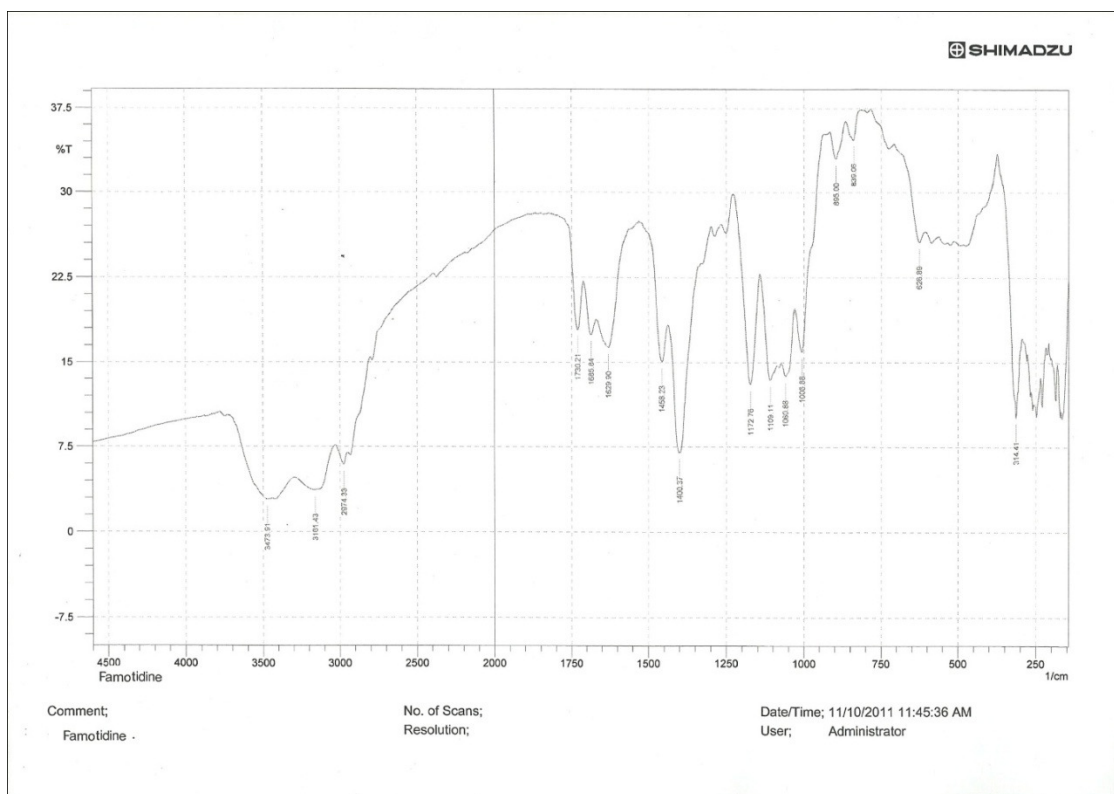


Figure 7.2 IR spectrum of sodium alginate

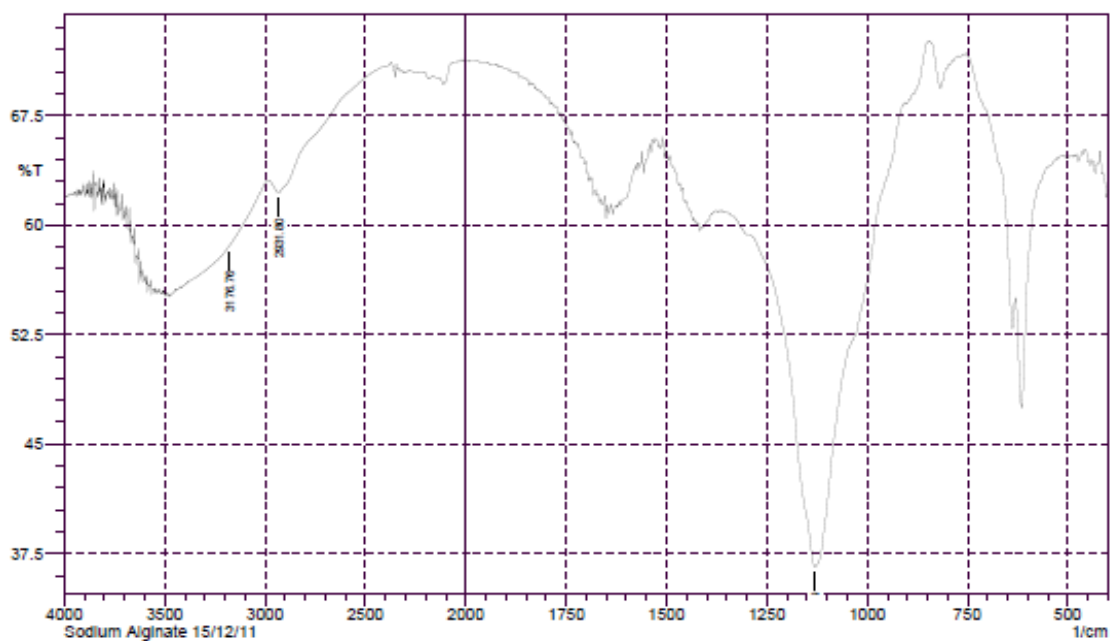


Figure 7.3 IR spectrum of HPMC K4M

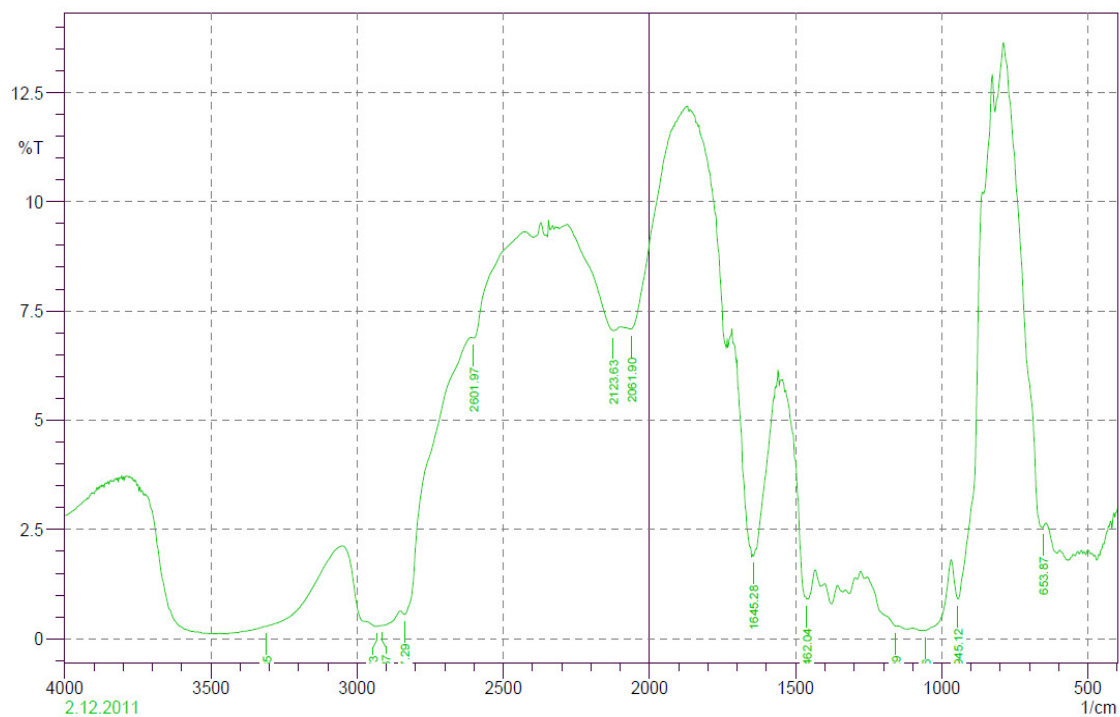


Figure 7.4 IR spectrum of carbapol

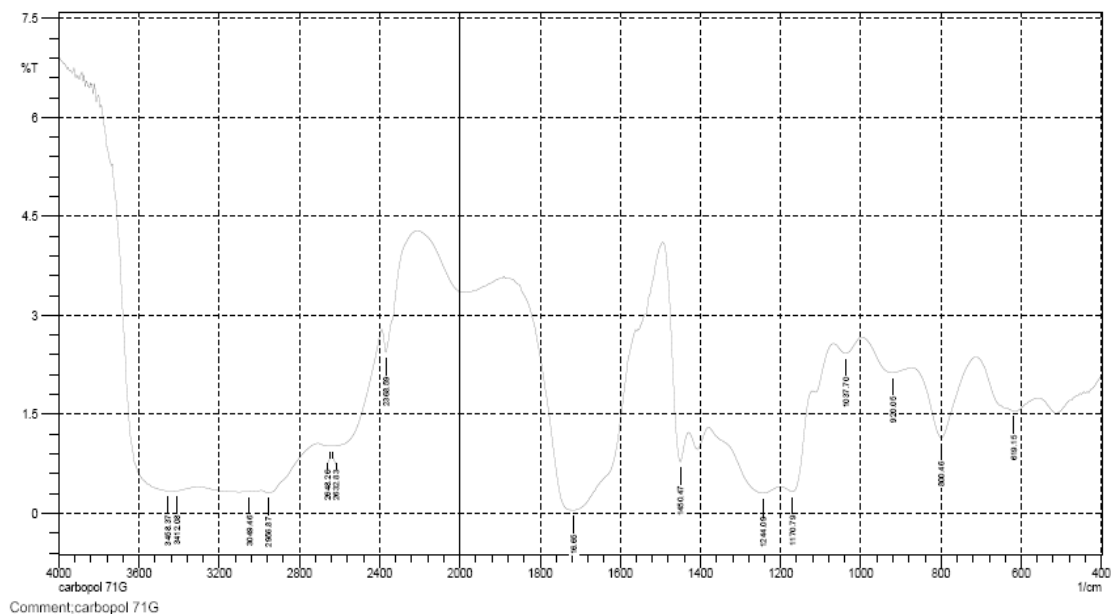


Figure 7.5 IR spectrum of pectin

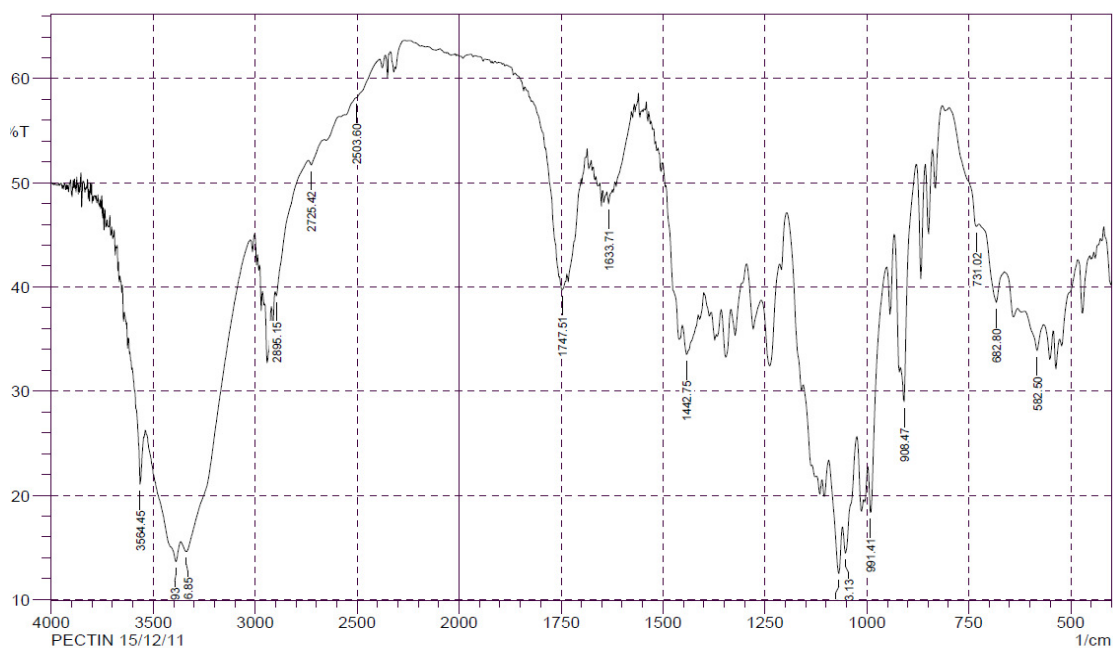


Fig 7.6 IR spectrum of sodium alginate, carbapol- FAMOTIDINE physical mixture

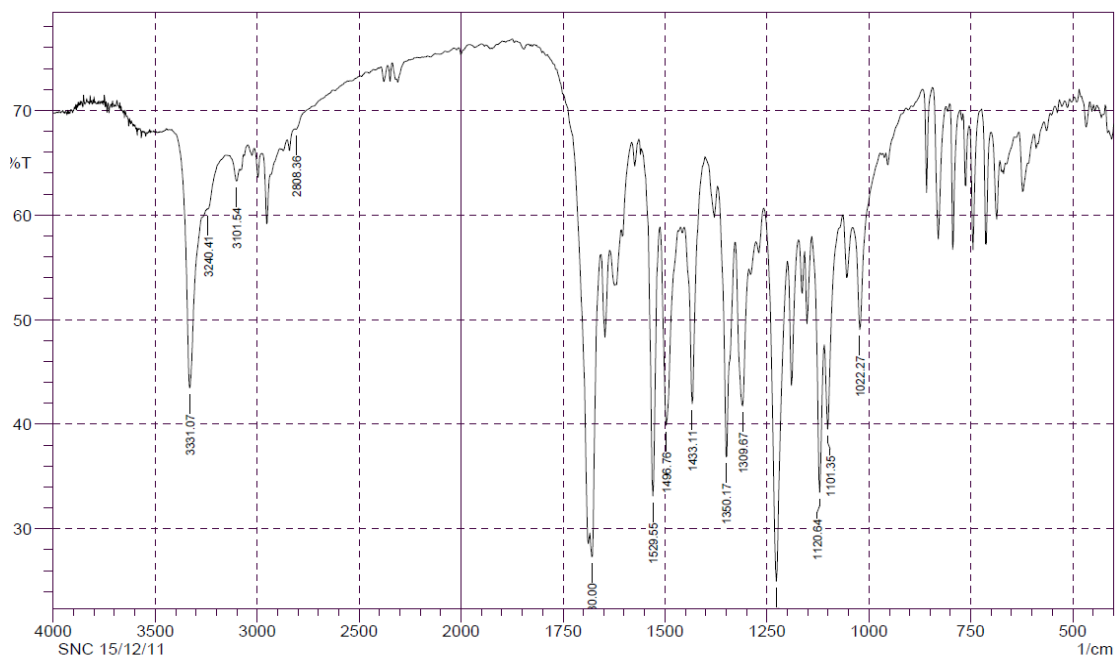


Fig 7.7 : IR spectrum of sodium alginate, pectin – FAMOTIDINE physical mixture

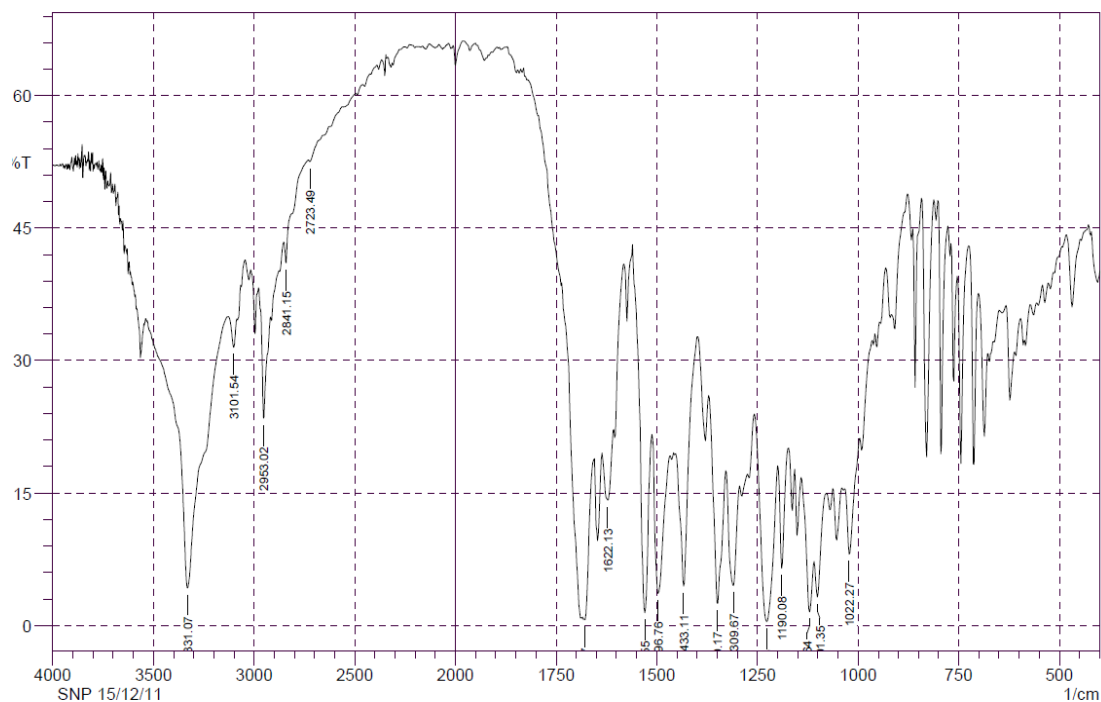
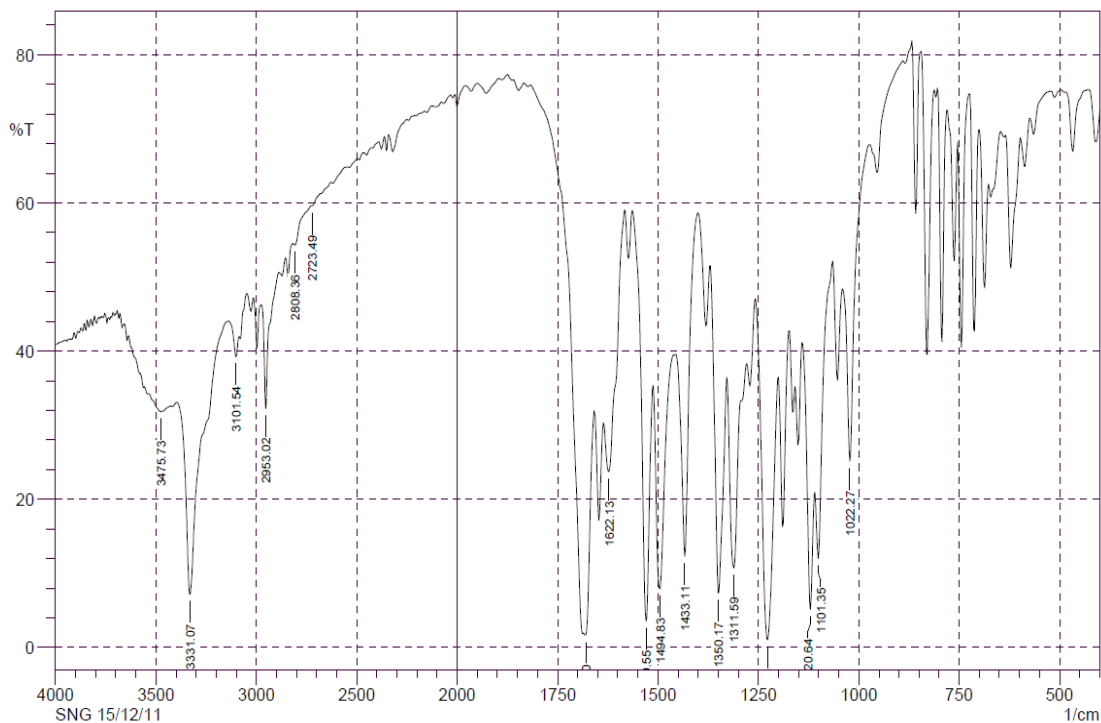


Fig 7.8 IR spectrum of Sodium alginate, – FAMOTIDINE physical mixture



ii) Development of solubility profile of selected drug (FAMOTIDINE) in various solvent used particles making procedure.

To know the solubility of the selected drug in polar, non- polar solvents and phosphate buffer, the solubility test was done in various organic solvents, distilled water and phosphate buffers. From the table (1) it is clear that the selected drug FAMOTIDINE is freely soluble in alcoholic solution, buffer solution and poorly soluble in water.

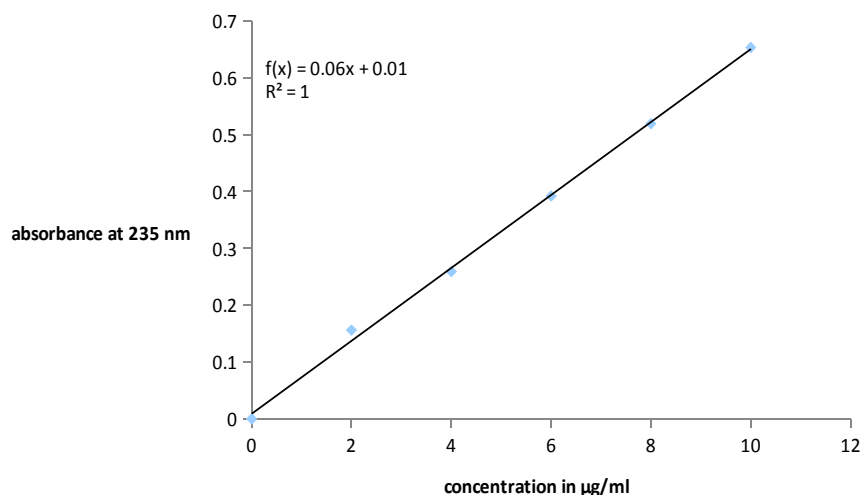
iii) Preparation of calibration curve:

Prepared calibration curve of drug FAMOTIDINE by using phosphate buffer (pH6.8).The drug absorbance was measured at 235 nm using UV double beam spectrophotometer. The linearity of the absorbance was found to be from the concentration between 2-10 μ g/ml ($r_2=0.9934$).

Table 7.2: calibration data of drug FAMOTIDINE by using phosphate buffer pH 6.8

Concentration in μ g/ml	Absorbance at 235 nm
0	0
2	0.156
4	0.259
6	0.392
8	0.519
10	0.653

Figure 7.11: Calibration curve of drug FAMOTIDINE by using phosphate buffer pH6.8



STAGE II: FORMULATION OF SODIUM ALGINATE MICRO BEADS BY IONOTROPIC GELATION AND CROSSLINKING METHOD.

I. General method of formulation of sodium alginate micro beads.

Micro beads prepared by ionotropic gelation and cross linking method. In this study micro beads were prepared by using sodium alginate alone and calcium chloride used as counter ion.

II. Optimization of process variables.

a) study on effect of different concentration of HPMC K4M as release modifier on sodium alginate micro beads:

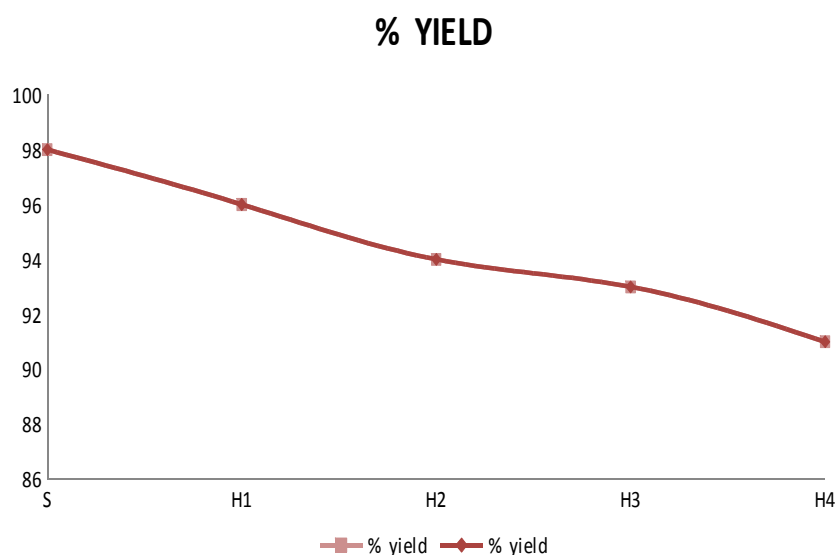
Four batches of micro beads coded such as (H₁, H₂, H₃ and H₄) were prepared by using sodium alginate and HPMC as coating polymer and they were evaluated for their percentage yield, drying rate, shape and size distribution through the optical microscope and swelling ratio.

Table (7.3) shows the effect of concentration of HPMC on beads formation.

Formulation code	% yield	Beads size in μm	Shape	Swelling ratio
S	98	1249.5 \pm 2.3	Discrete beads	1810.6 \pm 2.1
H ₁	95	1116.2 \pm 1.1	Discrete beads	1875.4 \pm 0.9
H ₂	94	1148.5 \pm 1.8	Discrete beads	1723.6 \pm 3.4
H ₃	93	1167.4 \pm 1.6	Aglomerate beads	1698.6 \pm 2.4
H ₄	91	1204 \pm 3.7	Aglomerate beads	1497 \pm 1.23

The percentage yields were in the range between 91-95%. The yields were slightly increased by increasing the concentration of sodium alginate and decreasing the concentration of HPMC K4M.

Figure 7.12 shows the effect of HPMC K4M on % yield



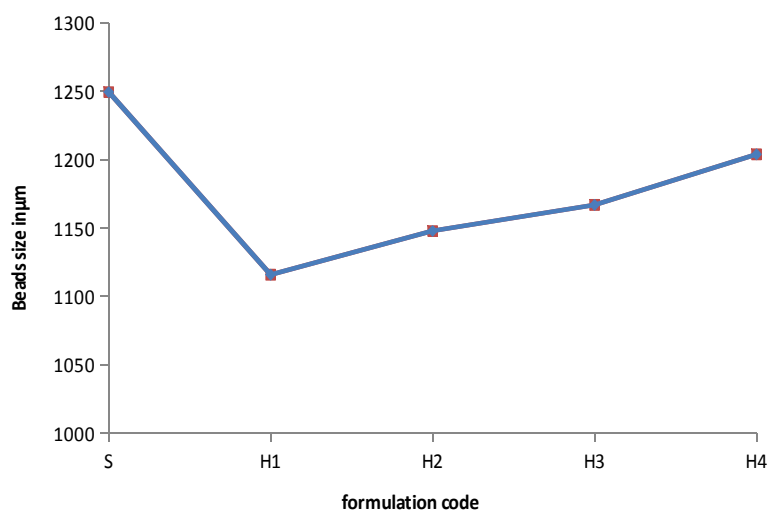
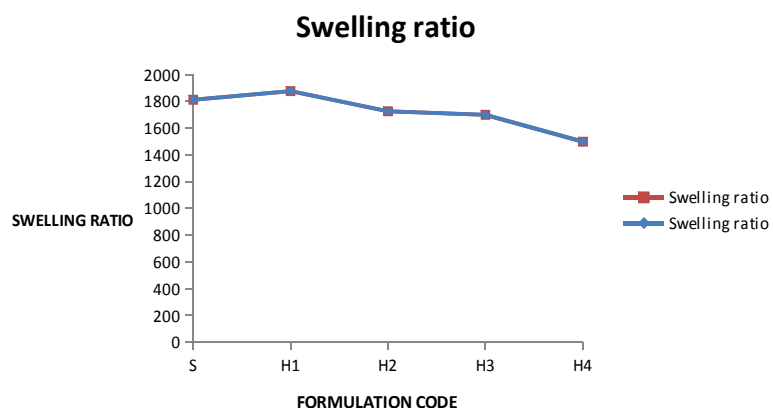


Figure 7.14 shows the effect of HPMC K4M on beads size

Swelling ratios were found to be in the range of 1497- 1810%. Swelling ratios were more by decreasing the concentration of coating polymer like HPMC K4M.

Figure 7.15 shows the effect of HPMC K4M on swelling ratio



Based on the high percentage yield, more swelling ratio, least size and good shape, micro beads prepared with 2% sodium alginate and 1% HPMC as release modifier coded as **H₁** was selected for drug loading.

b) **Study on effect of different concentration of Carbopol 71 G as release modifier on sodium alginate micro beads:**

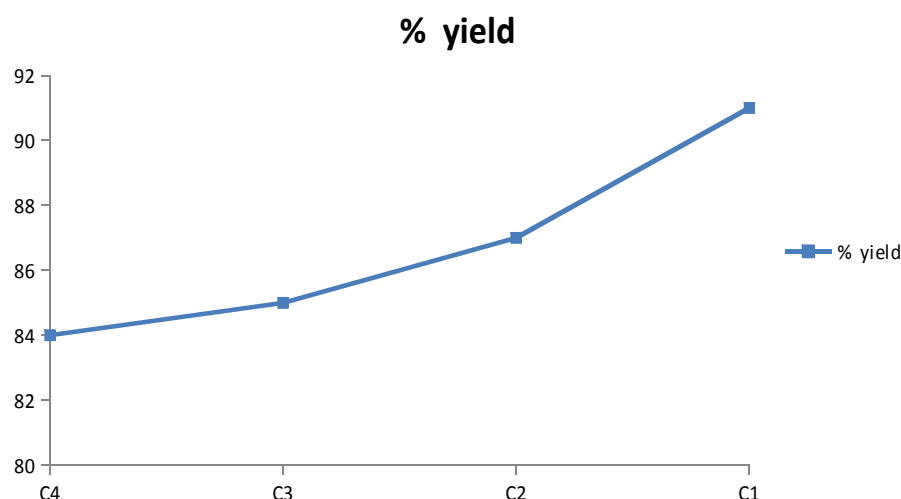
Four batches of micro beads coded such as (C₁, C₂, C₃ and C₄) were prepared by using sodium alginate and Carbopol 71 G as coating polymer and they were evaluated for their percentage yield, drying rate, shape and size distribution through the optical microscope and swelling ratio.

Table 7.4 shows the effect of concentration of Carbopol 71 G on beads formation.

Formulati on code	% yield	Beads size in μm	Swelling ratio	Shape of beads
C ₄	84	1257 \pm 3.1	1465 \pm 0.7	Aglomerate beads
C ₃	85	1249.6 \pm 1.9	1496 \pm 0.8	Aglomerate beads
C ₂	87	1215 \pm 2.37	1685 \pm 1.4	Discrete beads
C ₁	91	1138.8 \pm 1.9	1725 \pm 2.7	Discrete beads

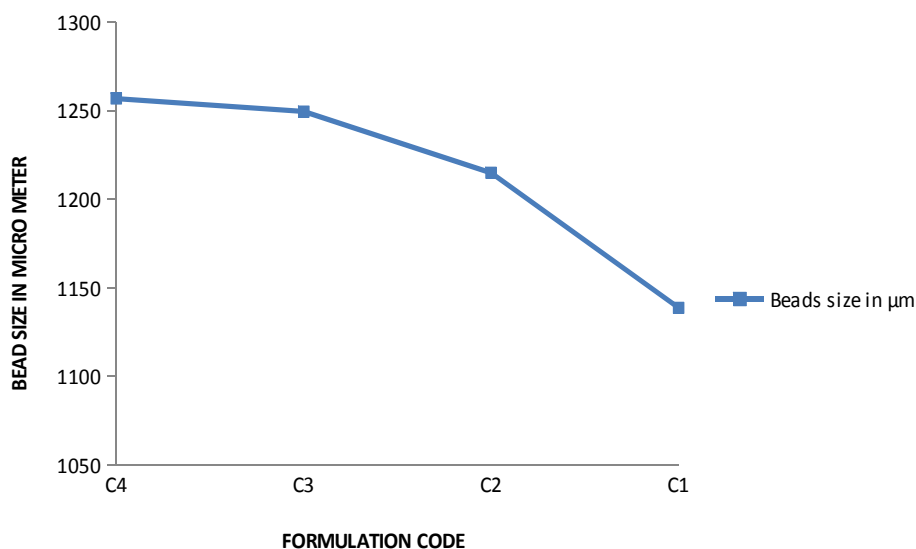
The percentage yields were in the range between 84-91%. The yields were slightly increased by increasing the concentration of sodium alginate and decreasing the concentration of Carbopol 71 G.

Figure 7.17 shows the effect of Carbopol 71 G on % yield



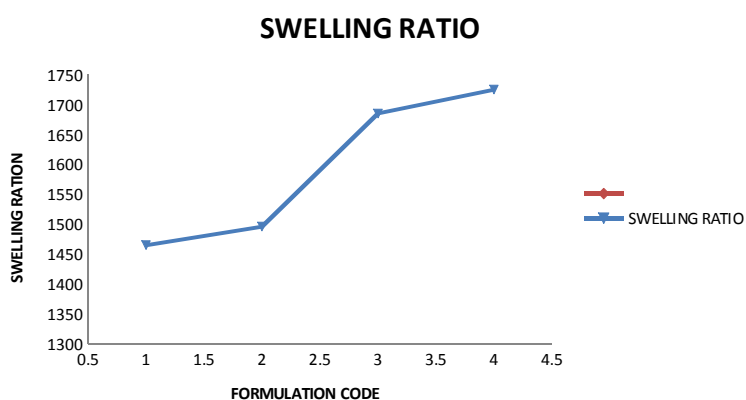
Beads shape and size distribution were found to be in the range of 1.1- 1.2 mm. Beads were clumped by increasing the concentration of coating polymer like Carbopol 71 G.

Figure7.19 shows the effect of Carbopol 71 G on beads size



Swelling ratio was found to be in the range of 1464- 1720%. Swelling ratio were more by decreasing the concentration of coating polymer like Carbopol 71 G.

Figure7.20 effect of Carbopol 71 G on swelling ratio



Based on the high percentage yield, more swelling ratio, least size and good shape, and lowest drying rate micro beads prepared with 1.75% sodium alginate and 0.25% Carbopol 71 G as release modifier coded as C₄ was selected for drug loading.

c) study on effect of different concentration of pectin as release modifier on sodium alginate micro beads

Four batches of micro beads coded such as (P₁, P₂, P₃ and P₄) were prepared by using sodium alginate and Pectin as coating polymer and they were evaluated for their percentage yield, drying rate, shape and size distribution through the optical microscope and swelling ratio.

Table 7.5 effect of concentration of Pectin on beads formation.

Formulation code	% yield	Beads size in μm	Drying rate/hr. at 50°C	Swelling ratio	Shape of beads
P4	74	1398.44 \pm 1.2	3.15	943 \pm 0.9	Aglomerate beads
P3	74	1379.9 \pm 1.9	2.45	1082 \pm 1.2	Aglomerate beads
P2	75	1246 \pm 1.2	2.10	1235 \pm 1.5	Discrete beads
P1	79	1201.23 \pm 0.8	1.45	1449 \pm 1.1	Discrete beads

The percentage yields were in the range between 73-78%. The yields were slightly increased by increasing the concentration of sodium alginate and decreasing the concentration of Pectin.

Figure 7.22 effect of Pectin on % yield

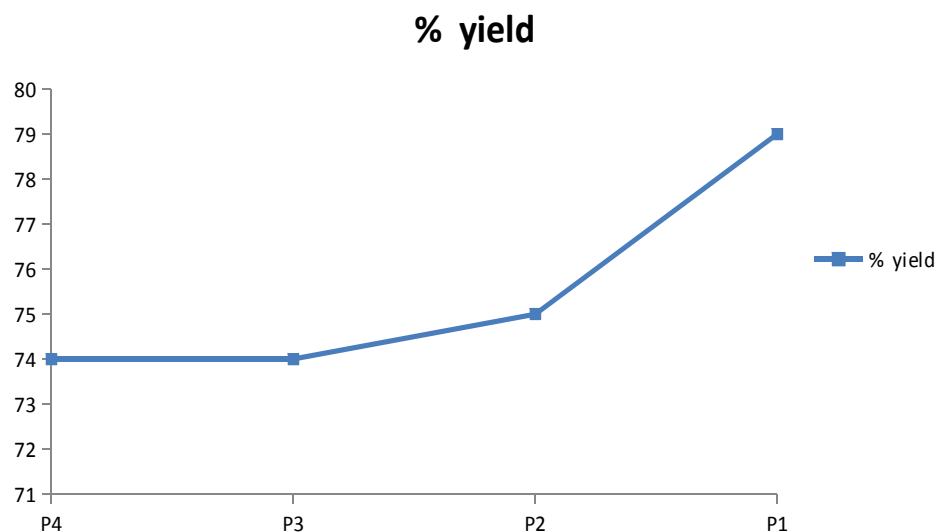
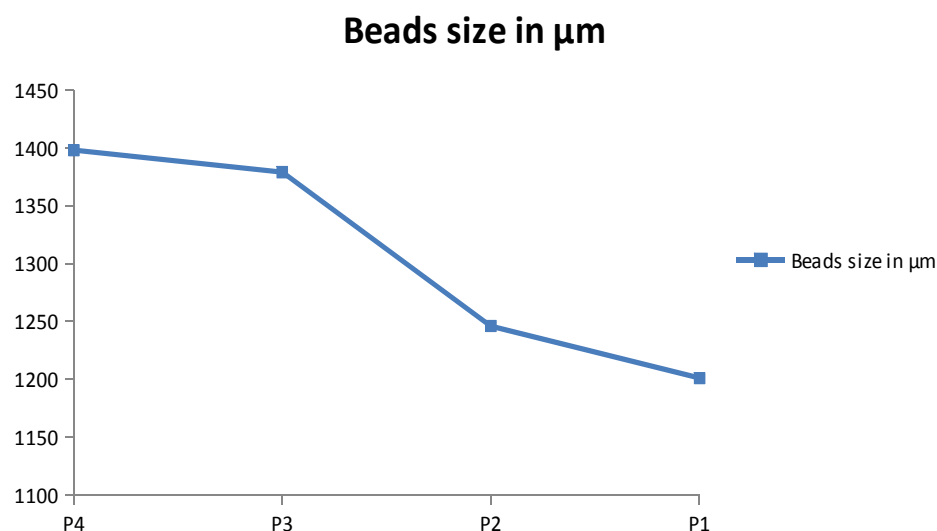
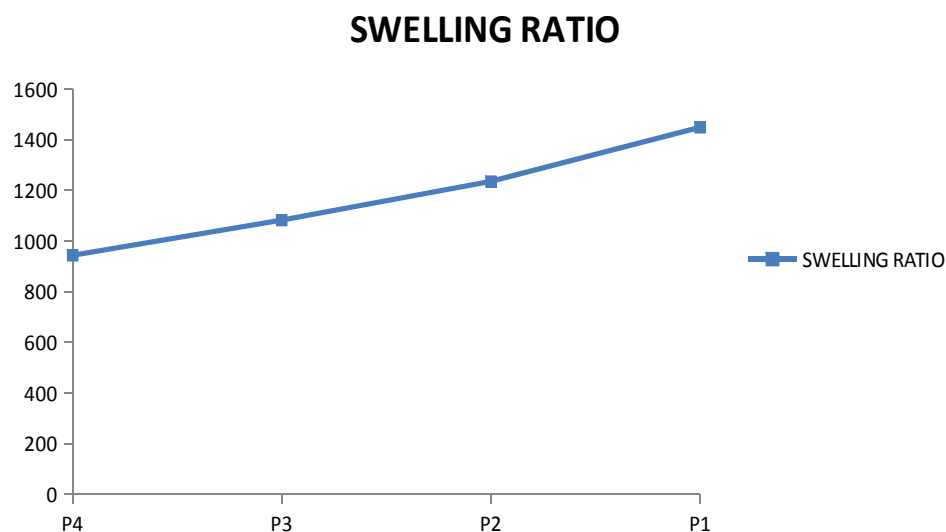


Figure 7. effect of Pectin on beads size



Swelling ratio was found to be in the range of 940-1444%. Swelling ratio were more by decreasing the concentration of coating polymer like Pectin.

Figure 7.25 effect of Pectin on swelling ratio



Based on the high percentage yield, more swelling ratio, least size and good shape, and lowest drying rate micro beads prepared with 2.0% sodium alginate and 1.0% Pectin as release modifier coded as **P₁** was selected for drug loading.

STAGE III: SELECTION OF OPTIMIZED VARIABLES FROM THE PLACEBO BEADS.

Based on the physicochemical parameters of the placebo beads (high percentage yield, least size of the beads, highest swelling index and lowest drying rate) the batches H₄, C₄, P₄ and G₄ have been selected for drug loading.

STAGE IV: OPTIMIZATION OF PROCESS VARIABLE FOR FORMULATION OF DRUG LOADED BEADS.

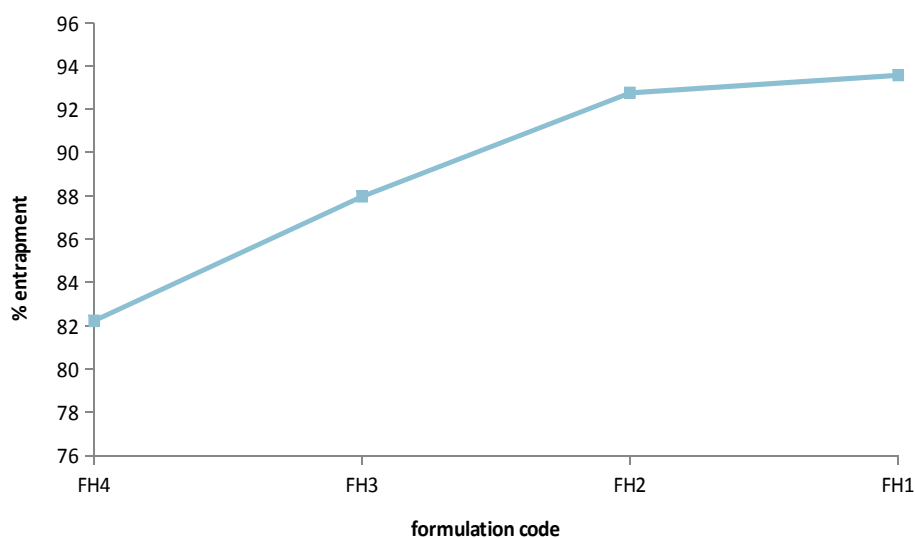
i) Study on effect of various concentration of drug (Famotidine) on HPMC K4M coated sodium alginate micro beads:

Four different concentration of Famotidine such as 10mg, 20mg, 30mg and 40 mg was added to the optimized batch of polymer coded as FH₁ and they were coded as FH₄, FH₃, FH₂ and FH₁ respectively and they were evaluated for their drug content, entrapment efficiency, loose surface crystal study and *in vitro* release study. The result showed that the highest percentage of drug content, entrapment efficiency and loose surface crystals were found to be produced by batch **FH₂**. Lowest percentage of drug content, entrapment efficiency and loose surface crystals were found to be produced by batch FH₄

Table (7.7) shows the effect of concentration of drug on HPMC K4M beads formation.

Formulation code	Amount Drug in mg/ 500mg of polymer	Beads size in mm	Swelling ratio at pH 6.8	Swelling ratio at pH 1.2	Entrapment efficiency (%)	LSC (%)
FH ₄	40	1214±1.5	1724	182	82.23±1.6	1.113
FH ₃	30	1252±1.8	1730	192	87.97±1.7	1.949
FH ₂	20	1182±0.9	1736	212	92.76±0.5	4.300
FH ₁	10	1212±1.3	1757	214	93.57±0.4	4.34

Figure 7.32 effect of concentration of drug on % entrapment of HPMC coated beads.



The *in vitro* release study of famotidine from micro beads were studied at $37 \pm 0.5^\circ\text{C}$ using phosphate buffer (pH 6.8) as the release medium. In vitro dissolution profiles of all the batches (FH1, FH2, FH3 and FH4) were studied for 24 hrs. The batch **FH₁** showed better sustained effect compared to other three batches.

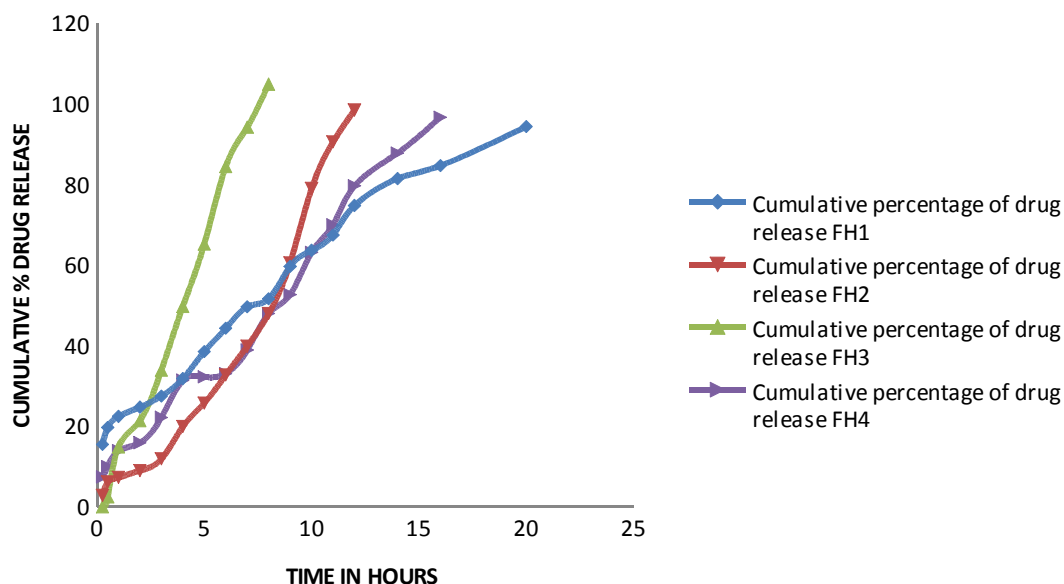
***In vitro* dissolution studies of Famotidine microbeads prepared by using HPMCK4M.**

Name of the drug	Famotidine
Dissolution medium	phosphate buffer pH6.8
Vol. of dissolution medium	900ml
Volume of sample withdrawn	5ml
Slope of calibration curve	0.064
R ² of calibration curve	0.9934

Table: 7.8 Cumulative percentage releases of micro beads prepared with sodium alginate and HPMC K4M as release modifier.

Time in hours	Cumulative percentage of drug release			
	FH ₁	FH ₂	FH ₃	FH ₄
0.25	15.45	2.761	-	7.37
0.5	19.65	6.126	2.421	9.966
1	22.40	7.26	14.816	13.878
2	24.67	8.94	21.36	15.87
3	27.43	11.84	33.87	22.13
4	31.76	19.87	49.68	31.34
5	38.45	25.69	65.12	32.178
6	44.23	32.67	84.34	32.99
7	49.56	39.78	94.10	38.81
8	51.56	47.89	104.79	47.89
9	59.57	60.45		52.56
10	63.56	78.90		63.04
11	67.34	90.45		69.87
12	74.67	98.34		79.55
14	81.34			87.67
16	84.56			96.56
20	94.23			

Figure7.33: In vitro dissolution profile of micro beads prepared with sodium alginate and HPMC K4M as release modifier.



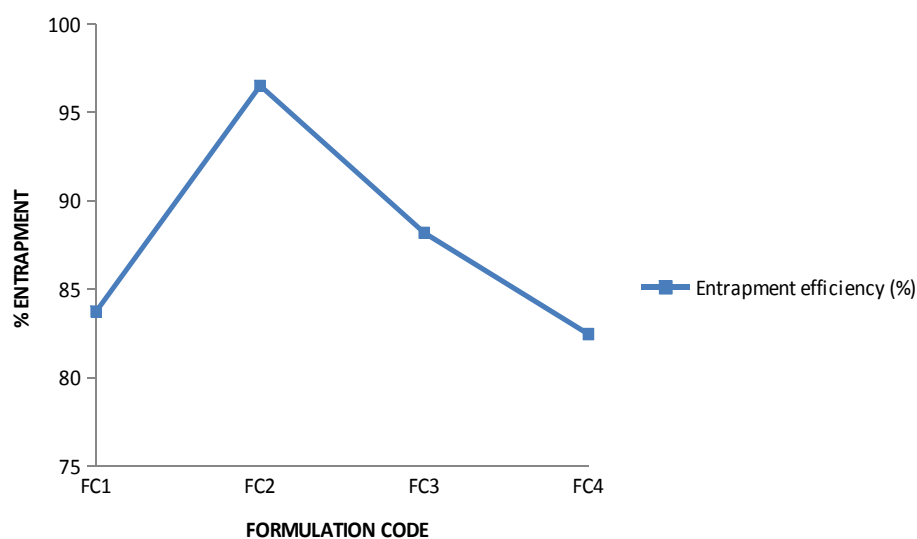
Study on effect of various concentration of drug (Famotidine) on Carbopol 71 G coated sodium alginate micro beads:

Four different concentration of Famotidine such as 10mg, 20mg, 30mg and 40mg was added to the optimized batch of polymer coded as C₄ and they were coded as FC₄, FC₃, FC₂ and FC₁ respectively and they were evaluated for their drug content, entrapment efficiency, loose surface crystal study and *in vitro* release study. The result showed that the highest percentage of drug content, entrapment efficiency and loose surface crystals were found to be produced by batch **FC₂**. Lowest percentage of drug content, entrapment efficiency and loose surface crystals were found to be produced by batch **FC₄**.

Table (7.9) effect of different concentration of drug on Carbopol 71 G coated beads formation.

Formulation Code	Amount Drug in mg/ 500mg of polymer	Beads size in mm	Swelling ratio at pH 6.8	Swelling ratio at pH 1.2	Entrapment efficiency (%)	LS C (%)
FC ₁	40	1017±1.7	2541	213	83.73±0.43	0.19
FC ₂	30	1006.3±2.1	2381	244	96.49±1.05	0.21
FC ₃	20	997.6±1.5	2185	153	88.18±0.43	0.15
FC ₄	10	973±2.2	1910	172	82.46±0.31	0.14

Figure7.34 effect of concentration of drug on % entrapment



***In vitro* dissolution study:**

The *in vitro* release study of famotidine from micro beads were studied at 37 ±0.5°C using phosphate buffer (pH 6.8) as the release medium. In vitro dissolution profiles of all the batches (FC₄, FC₃, FC₂ and FC₁) were studied for 24 hrs. The batch FC₂ showed better sustained effect compared to other three batches.

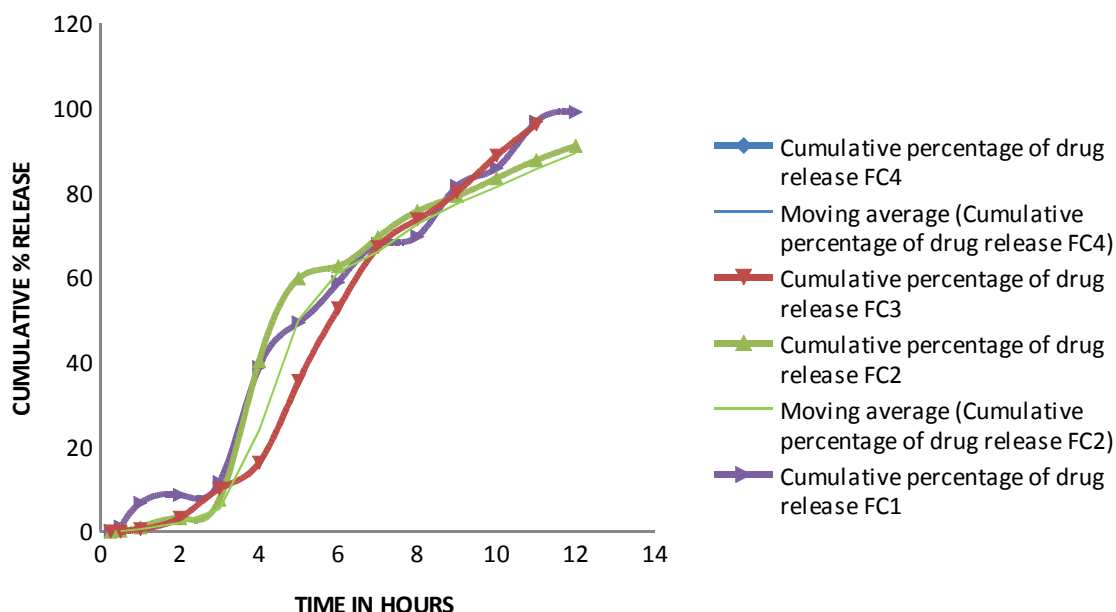
***In vitro* dissolution studies of Famotidine microbeads prepared by using Carbopol 71 G.**

Name of the drug	Famotidine
Dissolution medium	phosphate buffer pH6.8
Vol. of dissolution medium	900ml
Volume of sample withdrawn	5ml
Slope of calibration curve	0.064
R ² of calibration curve	0.9934

Table: 7.10 Cumulative percentage releases of micro beads prepared with sodium alginate and Carbopol 71 G as release modifier

Time in hours	Cumulative percentage of drug release			
	FC ₄	FC ₃	FC ₂	FC ₁
0.25	-	-	-	0.156
0.5	-	-	0.213	1.1345
1	3.34	0.581	0.988	6.786
2	4.517	3.24	3.137	8.678
3	12.623	10.12	7.567	11.678
4	52.75	16.24	40.23	38.81
5	66.73	35.52	59.78	49.34
6	93.66	52.66	62.67	58.87
7		67.12	69.46	67..90
8		73.67	75.67	69.67
9		80.12	79.23	81.56
10		88.75	83.43	85.83
11		96.08	87.67	96.78
12			91.07	99.02

Figure 7.35: In vitro dissolution profile of micro beads prepared with sodium alginate and Carbopol 71 G as release modifier



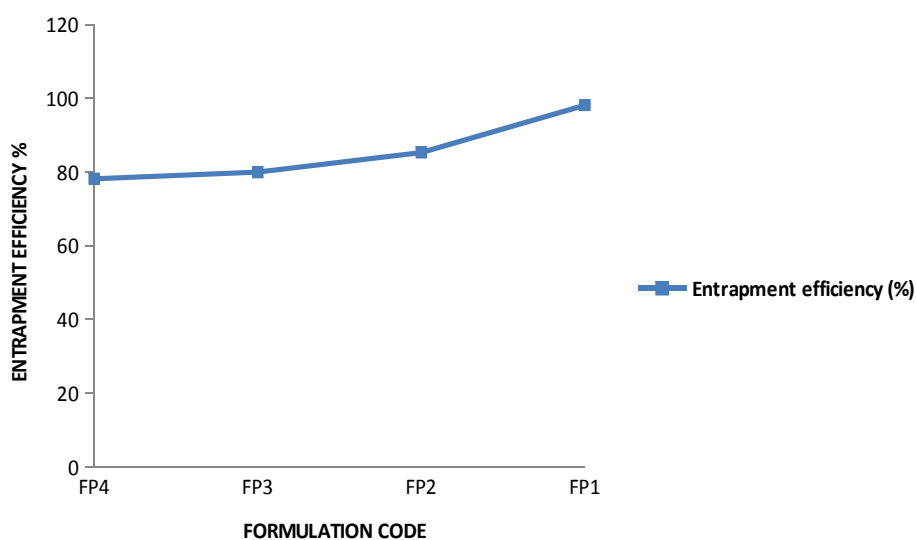
Study on effect of various concentration of drug (Famotidine) on pectin coated sodium alginate micro beads:

Four different concentration of Famotidine such as 5mg, 10mg, 20mg and 30mg was added to the optimized batch of polymer coded as P₄ and they were coded as F₉, F₁₀, F₁₁ and F₁₂ respectively and they were evaluated for their drug content, entrapment efficiency, loose surface crystal study and *in vitro* release study. The result showed that the highest percentage of drug content, entrapment efficiency and loose surface crystals were found to be produced by batch F₁₂. Lowest percentage of drug content, entrapment efficiency and loose surface crystals were found to be produced by batch F₉.

Table (7.11) shows the effect of different concentration of drug on pectin coated beads formation.

Formulation Code	Amount Drug in mg/ 500mg of polymer	Beads size in mm	Swelling ratio at pH 6.8	Swelling ratio at pH 1.2	Entrapment efficiency (%)	LSC (%)
FP ₄	40	1398±0.8	2214	221	78.16±1.84	1.949
FP ₃	30	1252±1.7	2298	236	79.91±1.2	1.113
FP ₂	20	1375±1.5	2331	245	85.26±0.58	4.300
FP ₁	10	1201±1.4	2364	244	98.12±0.33	4.34

Figure 7.36 shows the effect of concentration of drug on % entrapment



The *in vitro* release study of famotidine from micro beads were studied at 37 ±0.5°C using phosphate buffer (pH 6.8) as the release medium. In vitro dissolution profiles of all the batches (FP₁, FP₂, FP₃ and FP₄) were studied for 24 hrs. The batch FP₁ showed better sustained effect compared to other three batches.

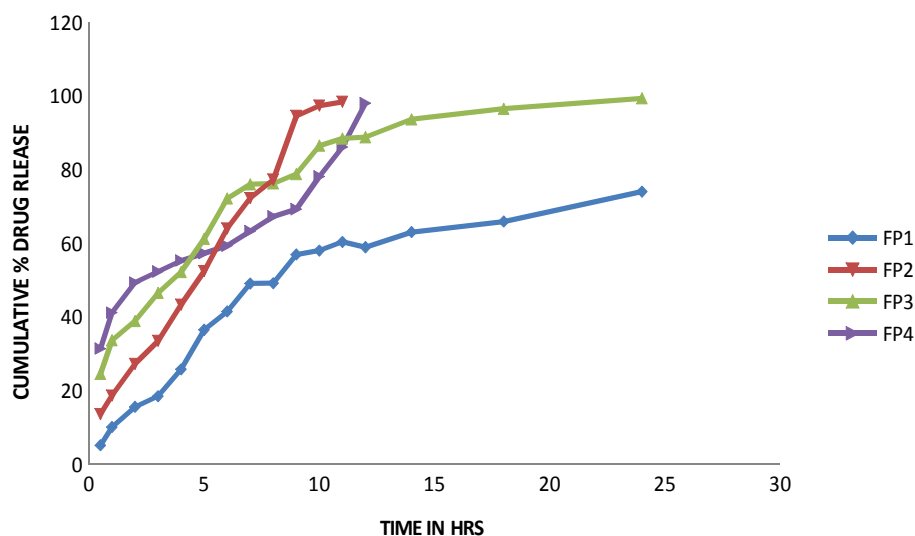
***In vitro* dissolution studies of Famotidine microbeads prepared by using Pectin.**

Name of the drug	Famotidine
Dissolution medium	phosphate buffer pH6.8
Vol. of dissolution medium	900ml
Volume of sample withdrawn	5ml
Slope of calibration curve	0.064
R ² of calibration curve	0.9934

Table: 7.12 Cumulative percentage releases of micro beads prepared with sodium alginate and Pectin as release modifier

Time in hours	Cumulative percentage of drug release			
	FP1	FP2	FP3	FP4
0.25	5.118	13.58	24.48	31.33
0.5	10.04	18.61	33.57	41.11
1	15.53	27.207	38.82	49.25
2	18.42	33.41	46.43	52.23
3	25.73	43.27	52.13	55.21
4	36.42	52.36	61.11	57.21
5	41.42	63.92	72.077	59.24
6	49.01	72.18	75.92	63.19
7	49.09	77.15	76.13	67.16
8	56.87	94.42	78.69	69.16
9	57.94	97.218	86.39	78.06
10	60.29	98.28	88.31	86.01
11	58.82		88.69	97.90
12	62.92		93.54	
14	65.79		96.39	
18	73.91		99.24	
24	98.64			

Figure 7.37 In vitro dissolution profile of micro beads prepared with sodium alginate and Pectin as release modifier



STAGE VII: IN VITRO RELEASE KINETIC STUDY ON SELECTED BATCH OF SODIUM ALGINATE MICROBEADS LOADED WITH FAMOTIDINE.

All the release data was fitted into various kinetic models like, zero order, first order, Higuchi, and Korsmeyer-Peppas, in order to find out order and mechanism of drug release from polymeric spheres.

Determination of order of release

Determined the order of release of drug from the selected batch of microbeads by graphical method from the dissolution data, a graph was plotted with % drug release remaining Vs time to find out zero order release. Linearity was observed and results are shown in the table (7.15) and figure (7.38-7.41)

Figure 7.40: order release of batch FH₁

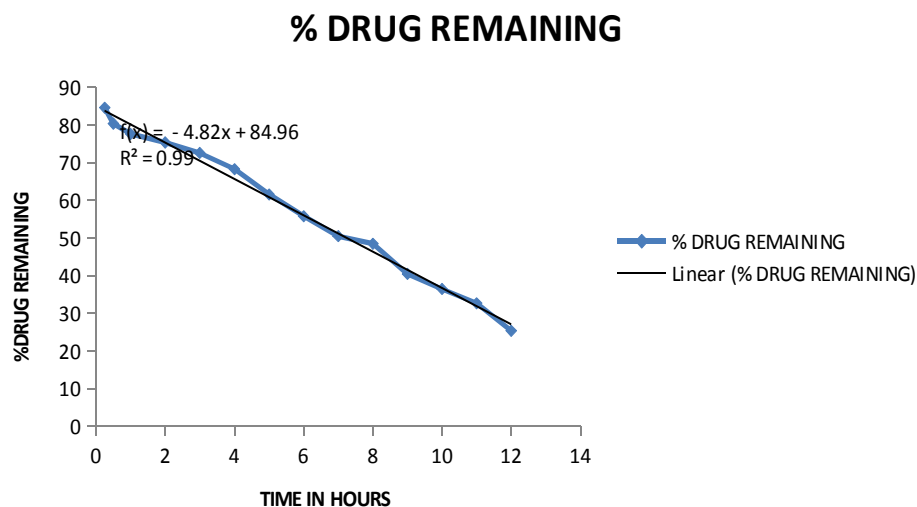


Figure7.41: order of release of batch FC₂

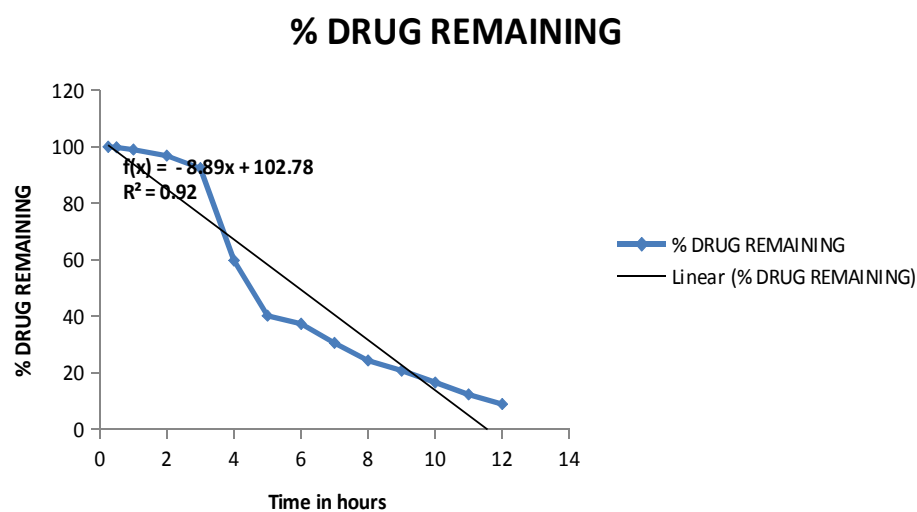


Figure 7.42: order of release of batch FP₁

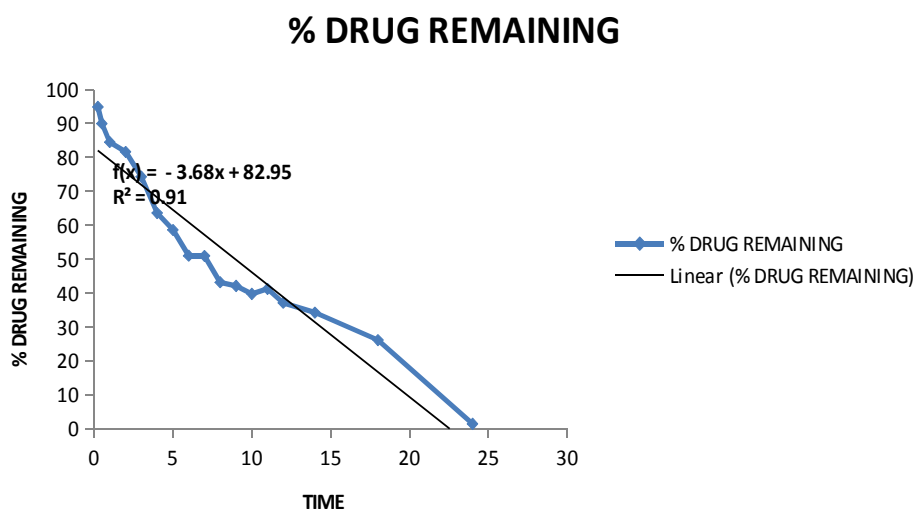
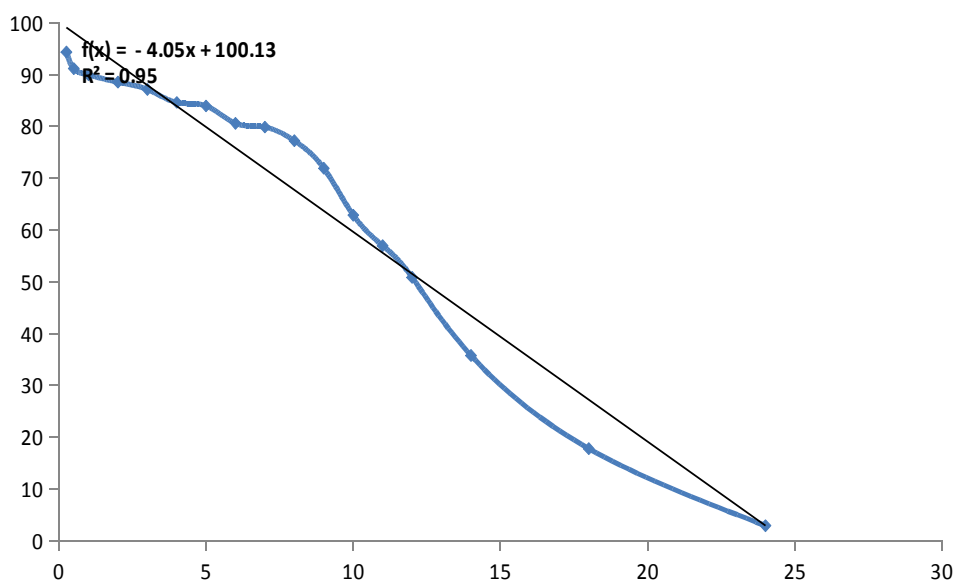


Figure 7.43: order of release of batch F₁₅



The result showed that all the selected batches of microbeads loaded with famotidine (FH₁, FC₂, and FP₁) followed zero order release.

Mechanism of release.

Determined the order of release of drug from the selected batch of microbeads by graphical method from the dissolution data, a graph was plotted with % drug release Vs square root of time to find out Higuchi diffusion mechanism and log % of release Vs log time to find out Korsmeyer Peppas's.

The value of 'n' gives an indication of the release mechanism; when $n = 1$, the release rate is independent of time (zero-order) (case II transport), $n = 0.5$ for Fickian diffusion and when $0.5 < n < 1.0$, diffusion and non-Fickian transport are implicated. Lastly, when $n > 1.0$ super case II transport is apparent. Regression coefficient and 'n' were calculated and is given in Table: (7.15) From the table, the value showed that, prepared micro beads exhibited zero order kinetics followed by super case -II transport.

Korsmeyer Peppas's. Graphs were plotted for selected batches (F_1, F_2, F_3 and F_4) and 'n' value was found to be > 1 . Therefore the mechanism was found to be super case II transport.

Figure 7.44: mechanism of release of batch FH₁

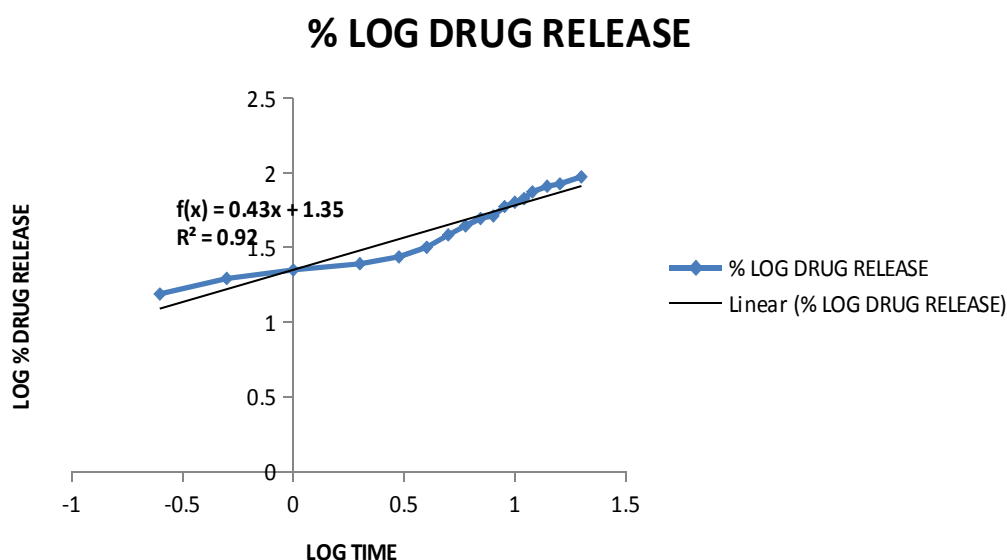


Figure 7.45: Mechanism of release of batch FC₂

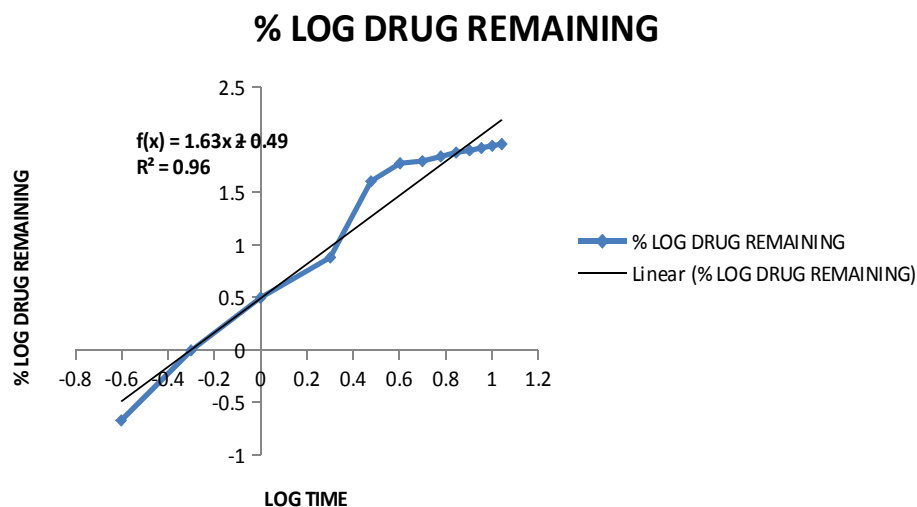


Figure 7.47: Mechanism of release of batch FP₁

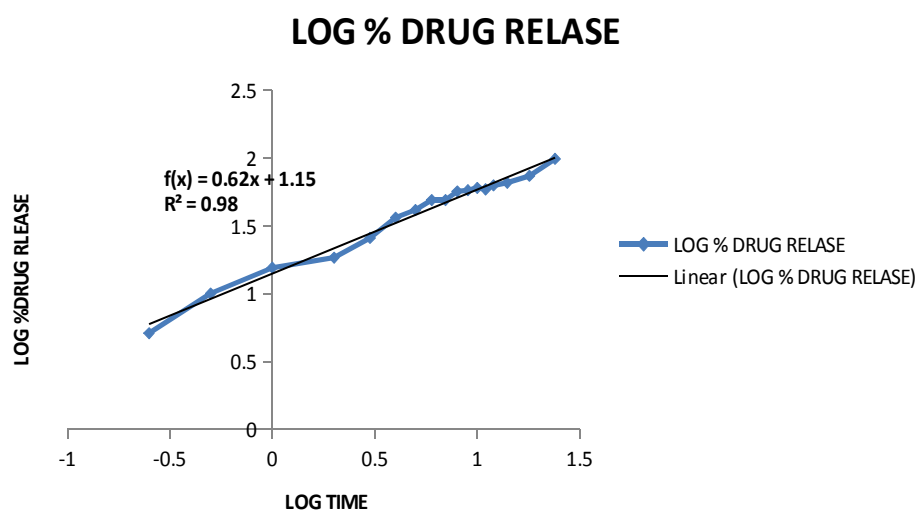


Table 7.15: model fitting data for in-vitro releases kinetic parameters of micro beads loaded with Famotidine.

Formulation code	Zero order (R ²)	Rate constant (K)	Korsmeyer peppas (R ²)	'n' values
FH ₁	0.993	4.822	0.923	1.351
FC ₂	0.923	8.890	0.957	0.491
FP ₁	0.953	4.048	0.984	1.148

STAGE VII: STABILITY STUDIES FOR BEST FORMULATION

In order to find out the stability of the drug loaded micro beads, selected and optimized batches of micro beads from each polymer containing known percentage of drug loading was stored at room temperature and it was observed for 45 days. The change in drug content was determined at an interval of 7 days. The morphology of the micro beads was also observed through optical microscope. Table (7.17) showed that the micro beads were stable at room temperature. The stability study revealed that there was no change in morphology and no change in drug content.

TABLE 7.16: Stability studies

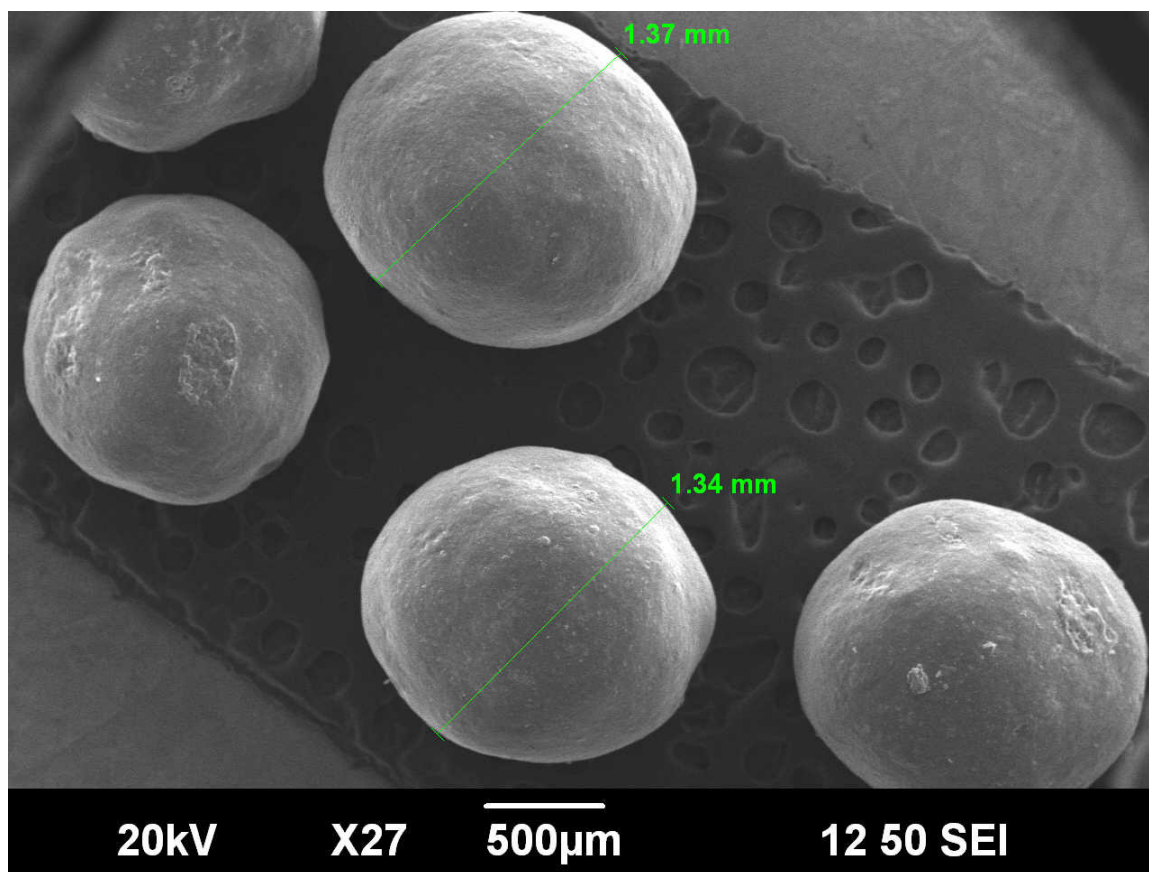
TIME IN DAYS	BEADS SIZE IN μM			%ENTRAPMENT		
	FH ₁	FC ₂	FP ₁	FH ₁	FC ₂	FP ₁
7	1172.5 \pm 1.1	1256 \pm 2.3	1089.2 \pm 1.4	90.57 \pm 0.5	82.73 \pm 0.4	99.1 \pm 0.3
15	1172.5 \pm 1.3	1256 \pm 2.1	1089.2 \pm 1.2	90.57 \pm 0.6	82.73 \pm 0.4	99.1 \pm 0.9
22	1172.5 \pm 0.3	1256 \pm 2.5	1089.2 \pm 0.9	90.57 \pm 0.7	82.73 \pm 0.4	99.1 \pm 0.7
30	1172.5 \pm 1.2	1256 \pm 2.1	1089.2 \pm 0.6	90.57 \pm 1.5	82.73 \pm 0.1	99.1 \pm 0.9
37	1172.5 \pm 1.48	1256 \pm 2.4 3	1089.2 \pm 0.9	90.57 \pm 0.5 2	82.73 \pm 0.4 9	99.2 \pm 1.1
45	1172.5 \pm 1.23	1256 \pm 1.3 5	1089.2 \pm 0.6	90.57 \pm 0.5 4	82.73 \pm 0.5 3	99.1 \pm 0.5

Time in days	Evaluated parameters						
	Beads size in μm				% entrapment		
	FH2	FC2	FP4		FH2	FC2	FP4
7	1172.5 \pm 1.1	1256 \pm 2.3	1089.2 \pm 1.4		90.57 \pm 0.5	82.73 \pm 0.4	99.1 \pm 0.3
15	1172.5 \pm 1.3	1256 \pm 2.1	1089.2 \pm 1.2		90.57 \pm 0.6	82.73 \pm 0.4	99.1 \pm 0.9
22	1172.5 \pm 0.3	1256 \pm 2.5	1089.2 \pm 0.9		90.57 \pm 0.7	82.73 \pm 0.4	99.1 \pm 0.7
30	1172.5 \pm 1.2	1256 \pm 2.1	1089.2 \pm 0.6		90.57 \pm 1.5	82.73 \pm 0.1	99.1 \pm 0.9
37	1172.5 \pm 1.48	1256 \pm 2.43	1089.2 \pm 0.9	800.8 \pm 1.2	90.57 \pm 0.52	82.73 \pm 0.49	99.2 \pm 1.1
45	1172.5 \pm 1.23	1256 \pm 1.35	1089.2 \pm 0.6	800.8 \pm 1.5	90.57 \pm 0.54	82.73 \pm 0.53	99.1 \pm 0.5

Scanning electron microscopy (SEM)

The morphological evaluation of the optimized micro beads formulation coded as F_{H1} was done by scanning electron microscopy (Figure). SEM study revealed that the microbeads were almost spherical in shape with rough outer surface.

Figure 7.49 shape and size of the beads (FH₁)



SUMMARY AND CONCLUSION

In the present study an attempt was made to formulate sustained release microbeads of Famotidine from sodium alginate with different release modifiers such as HPMC K4M, Carbopol 71G and Pectin so as to enhance bioavailability and to reduce dosing frequency of the selected drug.

- The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and also to achieve and maintain the desired drug concentration. This could be achieved through Multiparticulate dosage like beads which is divided into many individual units, so-called subunits, each exhibiting some desired characteristics.
- An attempt is made to develop microbeads by Ionotropic Gelation and cross linking Technique with a view to improve bioavailability, and also to reduce dose frequency and thereby to achieve an oral controlled release of the drug.
- From FT IR study, it was concluded that there was no interaction between polymers and drug. All the polymers used were compatible with the drug.
- Placebo beads were prepared by Ionotropic gelation and cross linking method by Using Sodium alginate and various types of different concentration of hydrophilic polymers such as HPMC K4m, Carbopol, and Pectin as release modifiers, Calcium chloride as counter ion and glutaraldehyde as cross-linking agent. Sixteen batches of placebo micro beads were prepared with different concentration of polymers and they were coded such as H₁, H₂, H₃, H₄, C₁, C₂, C₃, C₄, P₁, P₂, P₃, P₄, G₁, G₂, G₃ and G₄.
- All the prepared placebo beads were subjected to evaluation parameters like percentage yield, Particle size analysis, drying rate study and Swelling behavior.
- Percentage yield of beads were found in the range of 73-95%
- Particle size of gel beads were found in the range of 1103±0.8 to 1399±1.2µm.
- Swelling index of gel beads were in range of 940±0.9 to 1874 ±3.4 %

- Based on the highest percentage yield, and least beads size and high swelling index, few batches were selected for drug loading. Batches with 2% of sodium alginate and 1% of release modifier like HPMC K4M, Carbopol and Pectin.
- Drug loaded beads were prepared by same method and same polymer but only the difference was the concentration of drug FAMOTIDINE. Four different concentration of drug Famotidinesuch as 10mg, 20mg, 30mg & 40mg were added to the optimized batch of polymers.
- All the drug loaded beads were subjected to evaluation parameters like percentage drug entrapment, loose surface crystal study and in vitro release study. Based on the highest Percentage entrapment, more loose surface crystals and better sustained effect, the batches, like **FH₁**, **FC₂** & **FP₁** were found to be better than other batches.
- Selected batch such as **FH₁**, **FC₂** & **FP₁** weresubjected to *in vitro* release kinetic study, stability study and was found to exhibit zero order kinetics with release mechanism of super caseII-transport and they were found to be stable when stored at room temperature for 45 days
- Scanning electron microscopic study of selected batch **FH₁** was found out and it revealed that the microbeads were almost spherical in shape with rough outer surface.

CONCLUSION

In conclusion, ionotropic gelation and cross linking technique can be used for preparations of Famotidine micro beads from sodium alginate with other release modifiers like HPMC K4M, Carbopol 71G and Pectin. Prepared microbeads showed higher drug entrapment and prolonged release characteristics. Famotidine release from micro beads was influenced by the proportion of alginate and release modifiers.. The beads formed have a spherical shape with rough surface as evidenced by SEM. The result of *in vitro* release and release kinetic indicated sustained release and exhibited zero order kinetic followed by super case II- transport. Therefore, one can assume that the Famotidine micro beads are promising pharmaceutical dosage forms by providing sustaining effect and thereby improving the bioavailability. Therefore this developed sodium alginate micro beads with release modifier could be used as a carrier for the sustained delivery of other categories of drugs. The entire process is feasible in an industrial scale and demands pilot study.

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